INDIVIOR
Focus on you.

Symposium – ATHS Biarritz 2017

Opioid addiction:
a paradigm shift in patient treatment, optimising outcomes

Friday 20th October 2017, 12:00–13:00
Auditorium, Bellevue Congress Centre

This meeting has been organised and funded by Indivior

Date of Preparation: October 2017; Job Code: NBD-EU-P-1034-1708o

Faculty

Professor Marc Auriacombe, MD

Professor of Psychiatry and Addiction Medicine, Medical School of the University of Bordeaux, France and Adjunct Professor of Psychiatry at the University of Pennsylvania, Philadelphia, USA

Professor Roberto Ciccocioppo, MD

Professor of Pharmacology and Head of the International School of Advanced Study at the University of Camerino, Italy

Dr Jan Melichar, MD

Medical Director & Consultant Psychiatrist, Opioid Analgesia Dependency NHS Pilot, DHI, Bath and Consultant Psychopharmacologist, Glen Hospital, Bristol

Housekeeping

- Please turn mobile phones to silent
- Please remember to complete your evaluation forms to help us improve future educational meetings
- Discussions and questions are encouraged in the panel discussion at the end of the symposium

Programme

Time	Title	**Speaker**
12:00	Chair’s introduction	Prof. Marc Auriacombe, France
12:05	Craving and its correlation with successful treatment outcomes	Prof. Marc Auriacombe, France
12:20	Buprenorphine pharmacology: the basics revisited	Prof. Roberto Ciccocioppo, Italy
12:35	Improving quality of life through personalised care	Dr Jan Melichar, UK
12:50	Interactive discussion	All
13:00	Meeting close	

How to vote

- When a question appears on the screen, it will have numbered options
- Simply select your option and press the corresponding button
- If you wish to change your vote simply press your new selection
- Your last button pressed is the vote cast

Practice voting question

How many towns around the world is Biarritz twinned with?

A. 1

B. 3

C. 6

D. 8

Craving and its correlation with successful treatment outcomes

Professor Marc Auriacombe

Professor of Psychiatry and Addiction Medicine

University of Bordeaux, France

Disclosures

- D-A Pharma
- Lundbeck
- Indivior
- Gilead
- Bouchara

What is addiction? (or use disorder)

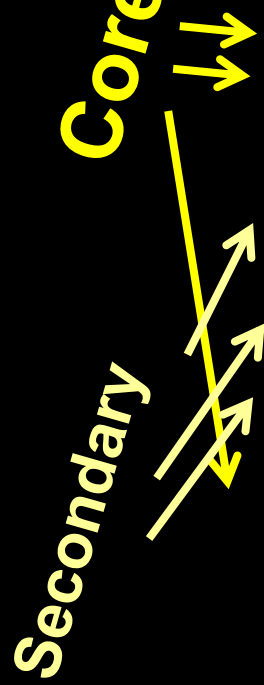
It’s not just using, even a lot

Opioid use disorder is a chronic medical condition affecting an estimated 1.3 million people across Europe

World Health Organization 1992; American Psychiatric Association 2013; European Monitoring Centre for Drugs and Drug Addiction 2016.

What is addiction?
Individual diagnostic criteria

- **ICD10 Dependence Syndrome**
  - **At least 3 of the following within a year**



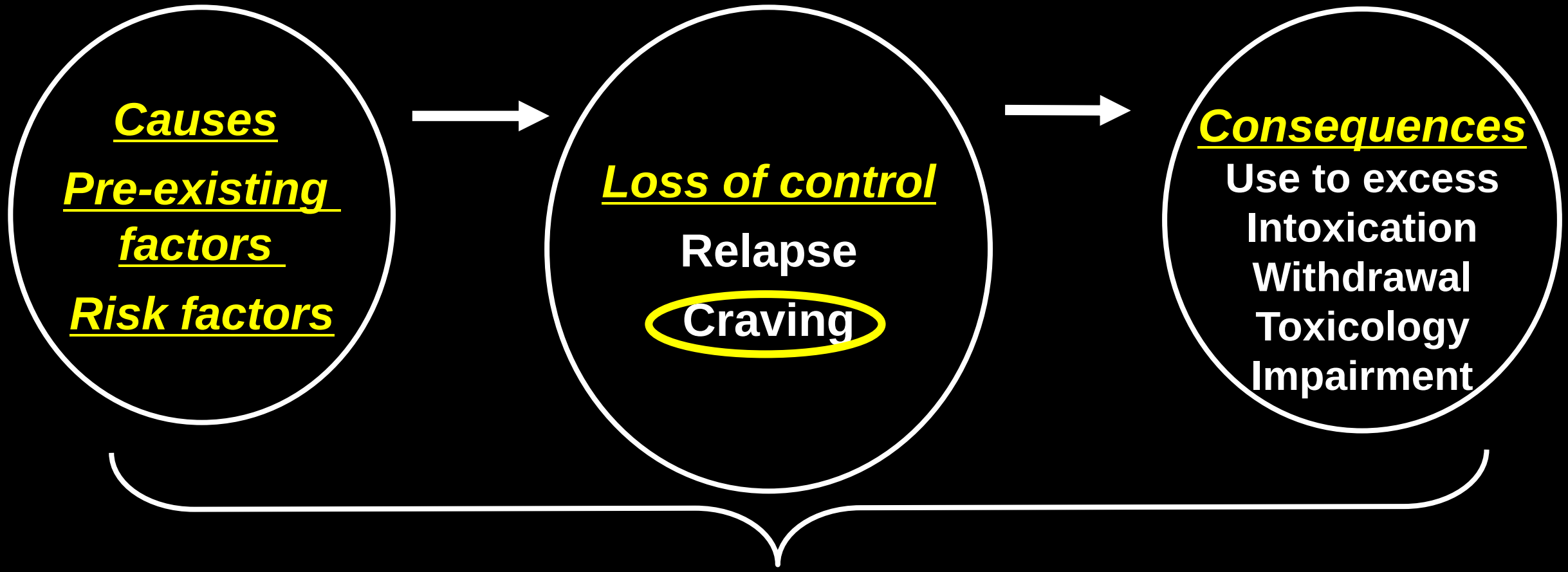
a) Compulsion to use
b) Use is difficult to control
c) Withdrawal syndrome
d) Tolerance
e) Persistent use despite negative consequences
f) Reduced time for gratifying activities not related to drug use and increased time in drug-use-related activities

- **DSM 5 Use Disorder**
  - **At least 2 of the following within a year**

1 Using more/longer than intended
2) Persistent desire/unsuccessful efforts to cut down
3) Time spent in substance activities
4) Craving
5) Failure to fulfill obligations
6) Neglect of important activities
7) Social/interpersonal substance-related problems
8) Hazardous use
9) Psychological/Physical use-related problems
10) Tolerance
11) Withdrawal

World Health Organization 1992; American Psychiatric Association 2013.

A core … and a constellation



Define addiction and its consequences, and distinguish it from use

Auriacombe M *et al. The Routledge Handbook of Philosophy and Science of Addiction* 2017 (in press).

Is craving a consequence or a cause to use?

?

Voting question

Do you routinely measure craving in your daily clinical practice?

1. **Yes**
2. **No**

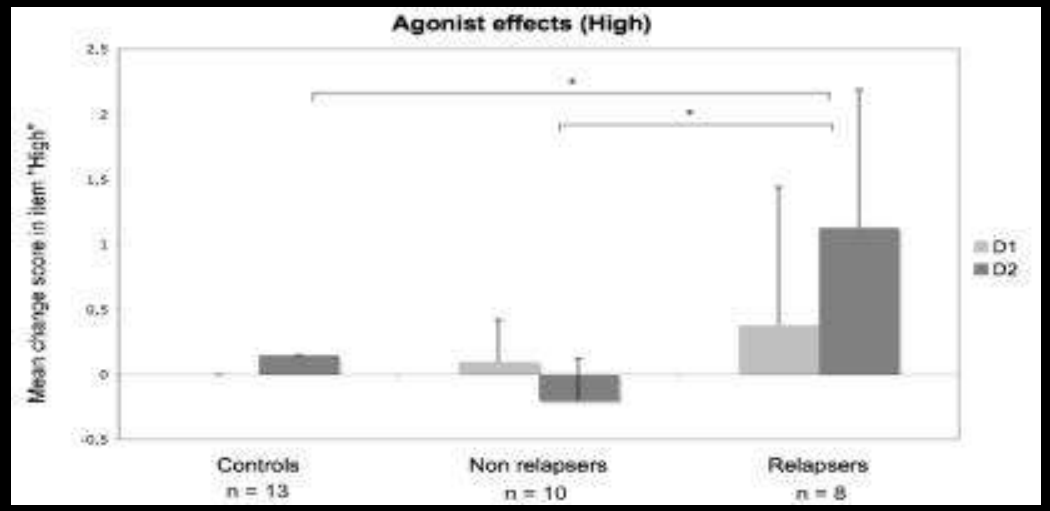
Craving predicts relapse

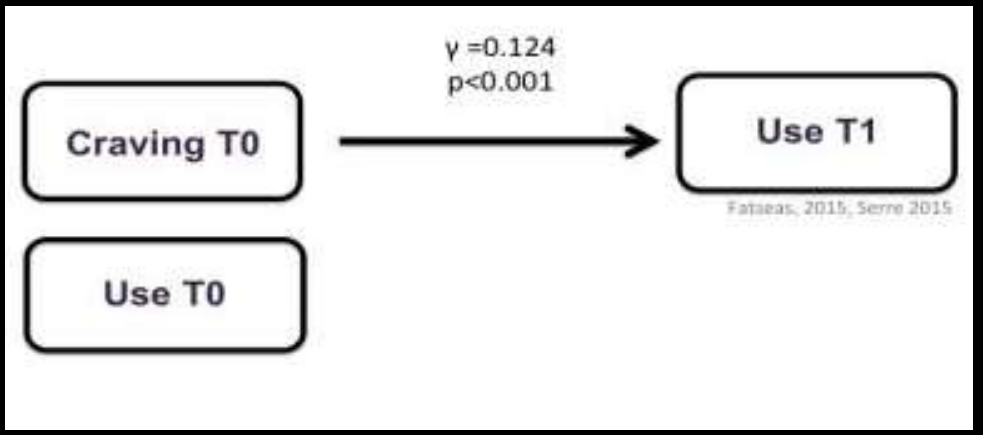
Over a period of months

3 months

Over a period of hours

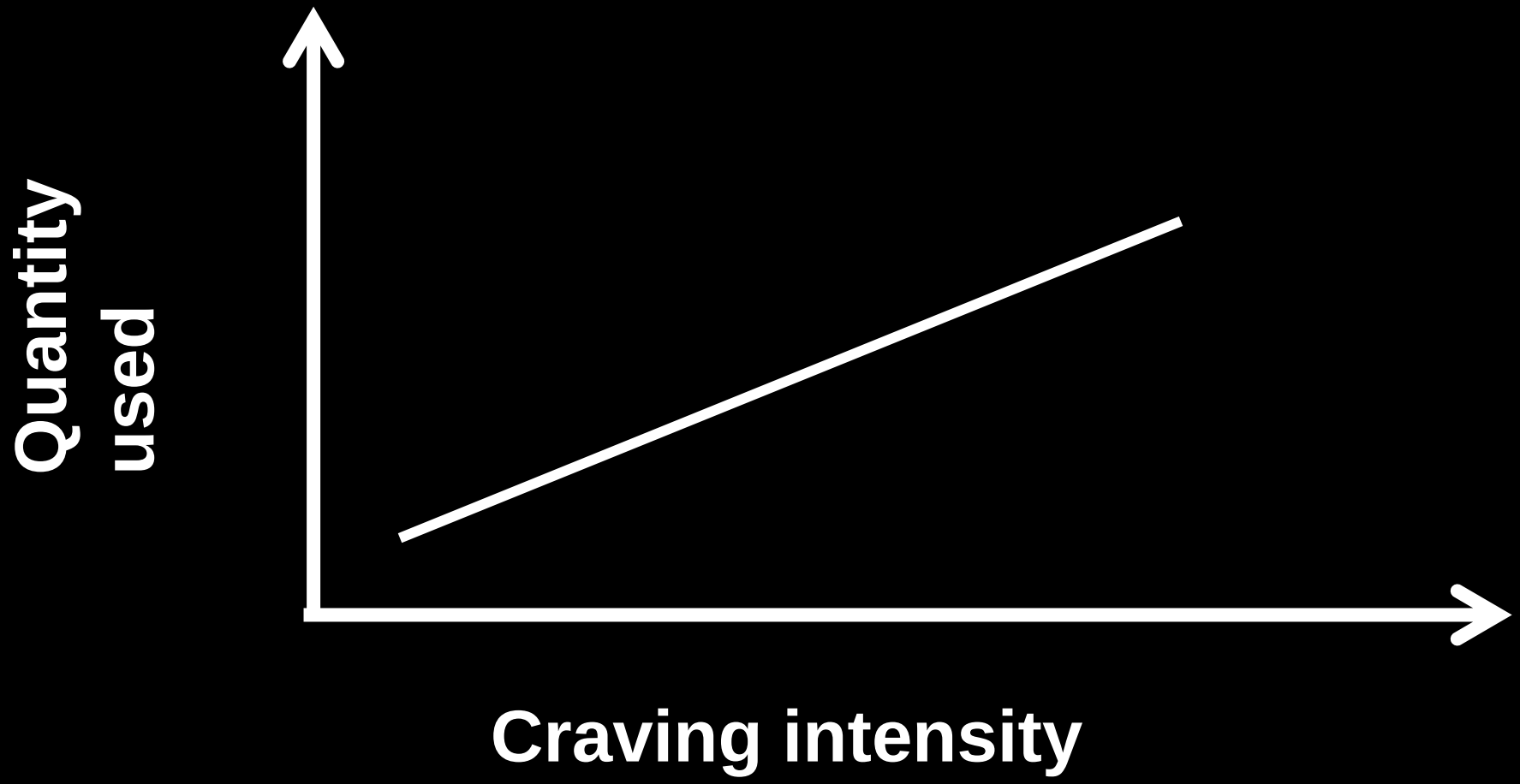
3 hours





Fatseas M *et al. Biol Psychiatry* 2011;70;720–7; Fatseas M *et al. Addiction* 2015;110;1035–42.

The craving-use relationship is dose-response



Fatseas M *et al. Addiction* 2015;110;1035–42; Serre F *et al. Drug and Alcohol Dependence* 2015;148;1–20; Enkema M, Bowen S. *Drug and Alcohol Dependence* 2017;179;1–7.

Let’s make it simple …

Addiction: a disease (disorder) …

An objective sign: Relapse

A predictor symptom: *Craving*

Is craving just an intense desire or urge?

Oh, by the way, what's the English for craving?

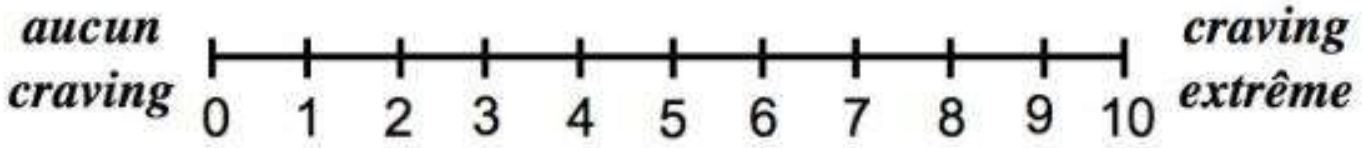
Unwanted craving

Tignol J. *Humeur* 1992;1:1–10; Tiffany S, Wray JM. *Ann N Y Acad Sci* 2012;1248;1–17; Sayette MA. *Annu Rev Clin Psychol* 2016;12;407–33; Auriacombe M *et al. Traité d'addictologie (2nd edition)* 2016;78–83; Auriacombe M *et al. The Routledge Handbook of Philosophy and Science of Addiction* 2017 (in press).

and it’s simple to measure

ÉVALUATION DU CRAVING

Défini comme une envie irrépressible de consommer et/ou comme la survenue de pensées obsédantes centrées sur l’objet d’addiction.



Objets d’addiction	Fréquence	Intensité moyenne	Intensité maximale
	Nombre de jours sur 30 derniers jours	(avec l’échelle) sur 30 derniers jours	(avec l’échelle) sur 30 derniers jours
1	…./30	…./10	…./10

Sayette MA. *Annu Rev Clin Psychol* 2016;12;407–33; Auriacombe M *et al. Traité d'addictologie (2nd edition)* 2016;78–83.

What should we do?

WHO International guidelines recommend that:

Treatment of opioid use disorder should include pharmacological and psychosocial interventions

Treatment is aimed at:

- **Reducing or ceasing opioid use**
- **Preventing future harm associated with opioid use**
- **Improving quality of life and well-being for people with opioid use disorder**

How can we best achieve those aims?

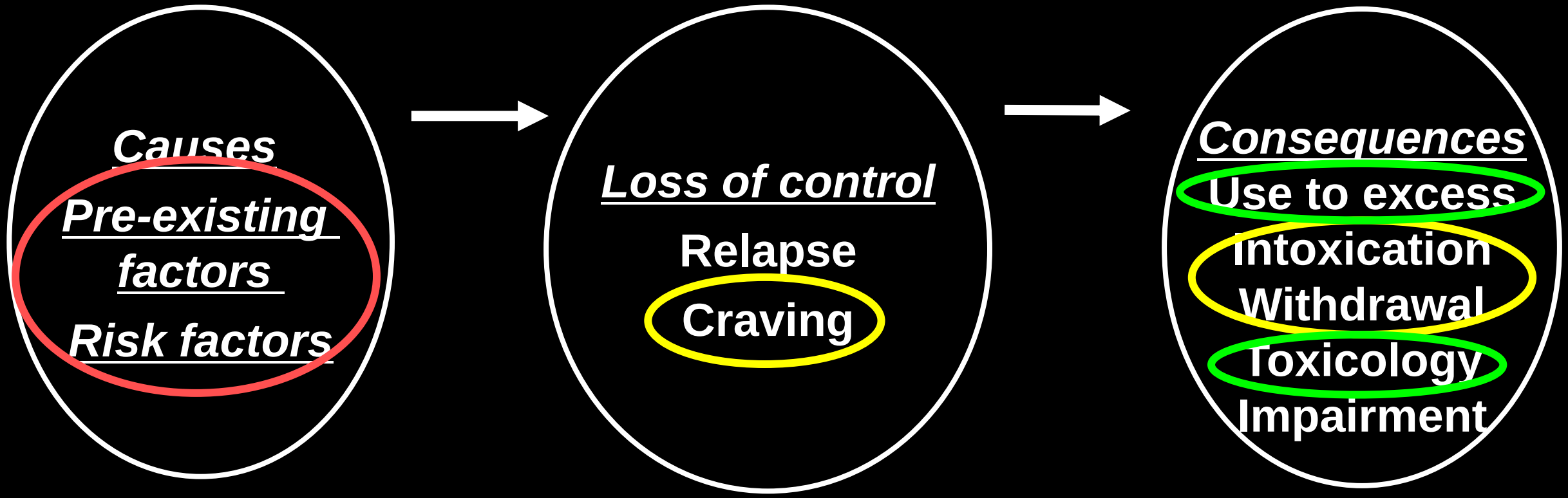
Clarified goals for medications

- **Primary goal**
  - **Avoid relapse**
  - **Manage and reduce craving**

- **Secondary goal**
  - **Minimise opiate withdrawal symptoms**

Auriacombe M *et al. Traité d'addictologie (2nd edition)* 2016;78–83; Daulouède JP, Auriacombe M. *Alcoologie et Addictologie* 2004;26:142S–8S; Fatseas M *et al. Traité d'addictologie (2nd edition)* 2016;751–60.

Treatment targets

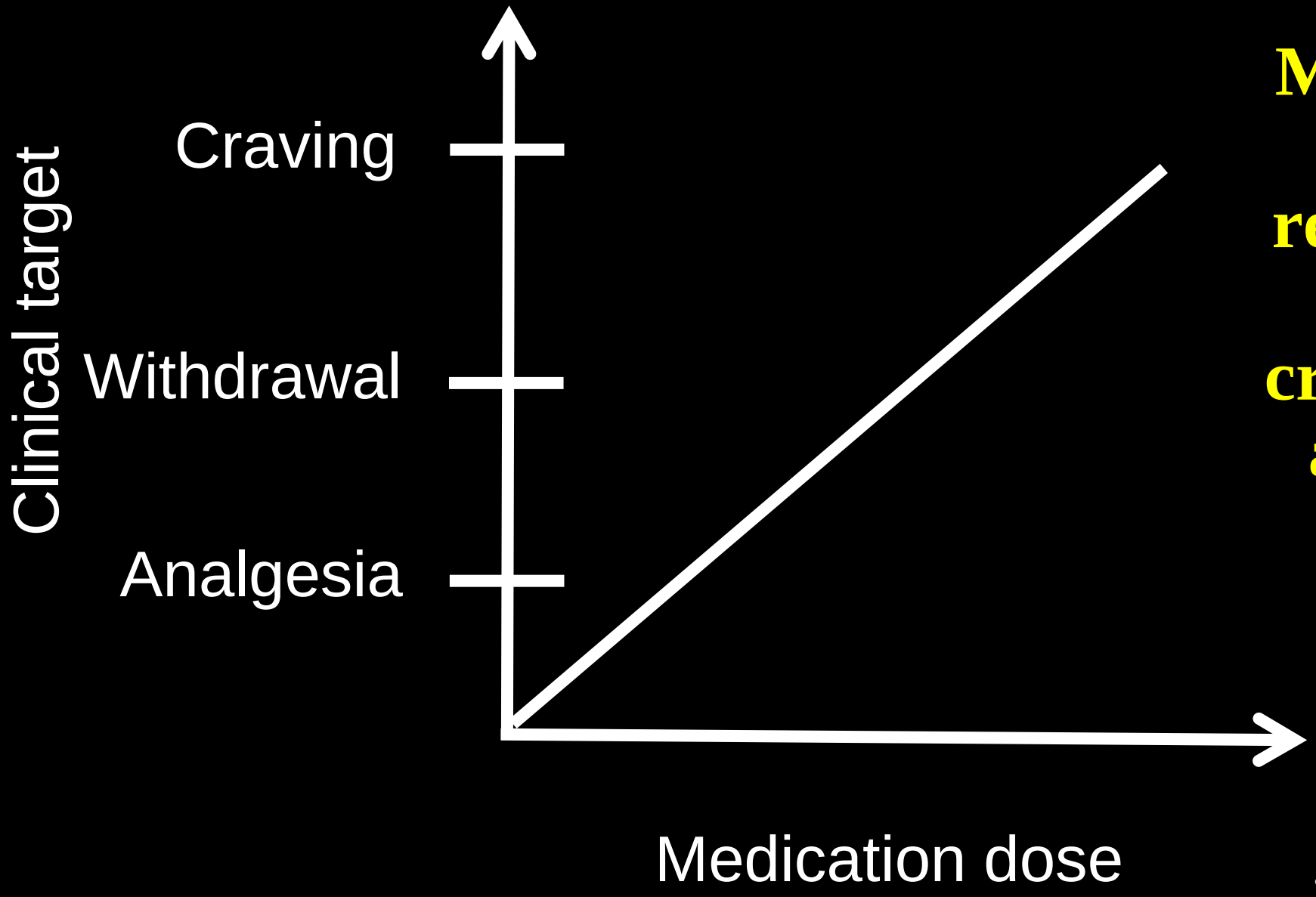


Methadone and buprenorphine

Psychotropic medications

A little medication and lots of psychotherapy

Auriacombe M *et al. The Routledge Handbook of Philosophy and Science of Addiction* 2017 (in press);
Auriacombe M *et al. Ann Med Interne* 1994;145;3–27;
Auriacombe M. *Dictionnaire des Concepts* 1997;1;426–30.



Medication efficacy on drug use reduction/abstinence is mediated by craving reduction in a dose-dependent relationship

Fareed A *et al. Am J Drug Alcohol Abuse* 2010;36:332–41; Fareed A *et al. J Addict Dis* 2011;30:27–38; Fareed A *et al. J Addict Dis* 2012;31:8–18; Fareed A *et al. J Addict Med* 2014;8:345–50; Auriacombe M *et al.* In: Reynaud M *et al. Traité d'addictologie* (2e édition) 2016;307–10.

To conclude … and go on

- Clarify treatment targets
  - Confirm addiction
  - Clarify comorbidities: psychiatric and medical
- Control treatment success by optimal medication management and counseling
  - Appropriate counseling for craving monitoring
  - Appropriate dosing to manage craving
- … and most importantly
  - Share information with patients

Thank you

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Université de Bordeaux

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Buprenorphine pharmacology: the basics revisited

Professor Roberto Ciccocioppo
School of Pharmacy
University of Camerino, Italy

Date of Preparation: October 2017; Job Code: NBD-EU-P-1034-1708q

Disclosures

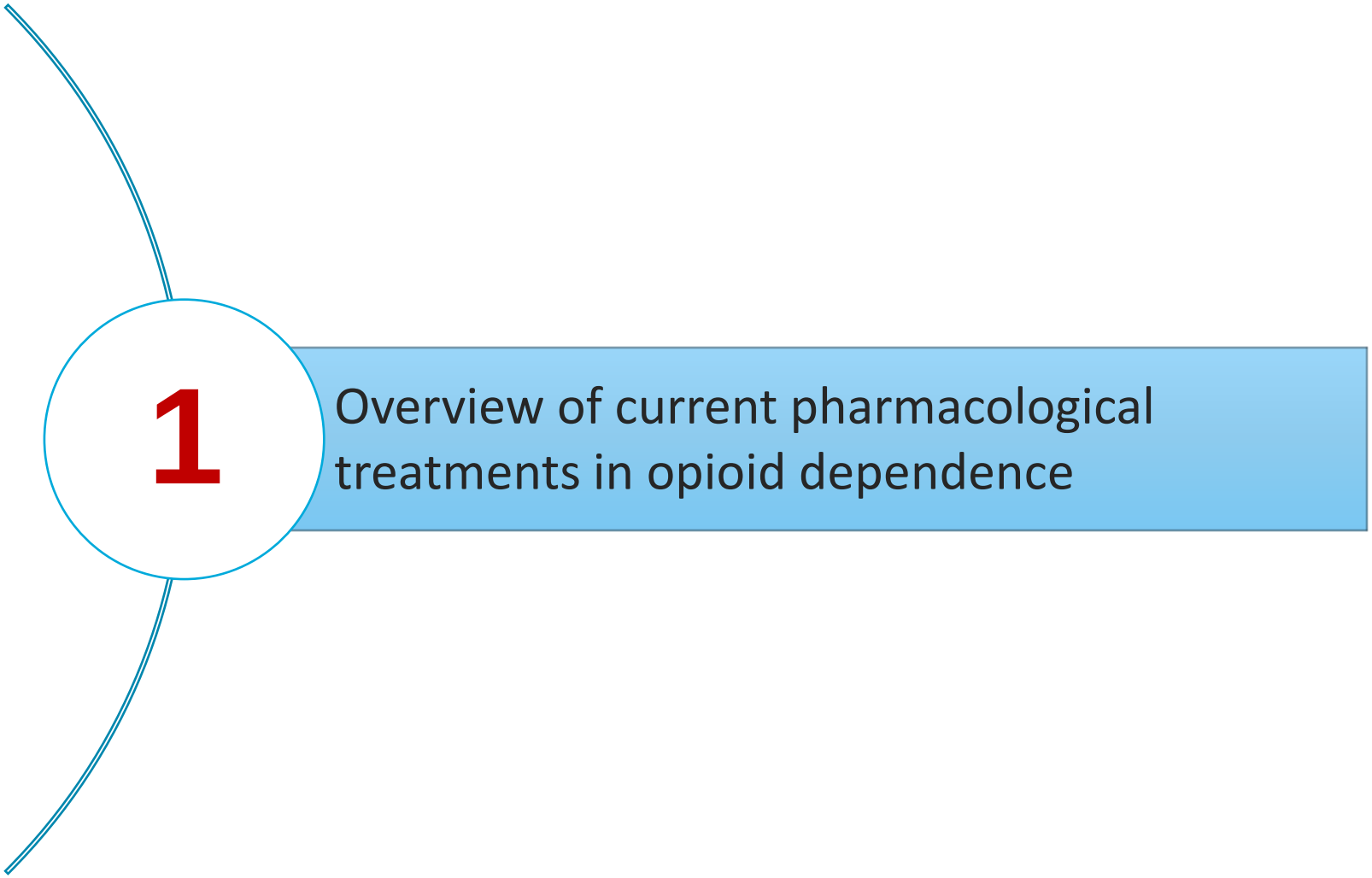
- Professor Ciccocioppo is the inventor of a number of patent applications, which have been assigned to Omeros, relating to the therapeutic use of PPARg agonists in addiction. He is entitled to receive royalties from Omeros under such licensing arrangement

- Previous and current consultancy activities for Omeros Corporation, Takeda, Mitsubishi Tanabe, FB-Health, Cerevance

Objectives

1. Overview of current pharmacological treatments in opioid dependence
2. The pharmacodynamic effects of opioid receptor occupancy
3. Linking buprenorphine pharmacology to clinical outcomes

Objective


1
Overview of current pharmacological treatments in opioid dependence

Approved treatments in opioid addiction

TYPE OF TREATMENT	ADVANTAGES	DISADVANTAGES
Maintenance treatment (methadone, buprenorphine, SROM)	Strong evidence of capacity to: ✓ Reduce opioid use ✓ Decrease mortality ✓ Improve quality of life Capacity to retain patients in Rx	Expense to patient (daily travel dispensing fees) Side effects, stigma Prolonged withdrawal on cessation
Detoxification	Short-term commitment Attractive to consumer Low threshold easy access Entry point to treatment	Poor long-term outcomes if stand-alone treatment Increased overdose risk following withdrawal Can lead to destabilisation of other health conditions
Antagonist treatment (naltrexone, naloxone)	Effective in decreasing opioid use in highly motivated well-supported people Opioid-free medication	Poor retention for most people Limited acceptance Complicates pain management Cost to patient Requires detoxification prior to initiating naltrexone Increased risk of overdose

SROM, slow-release oral morphine

Minozzi S *et al. Cochrane Database Syst Rev* 2011;13(4):CD001333.

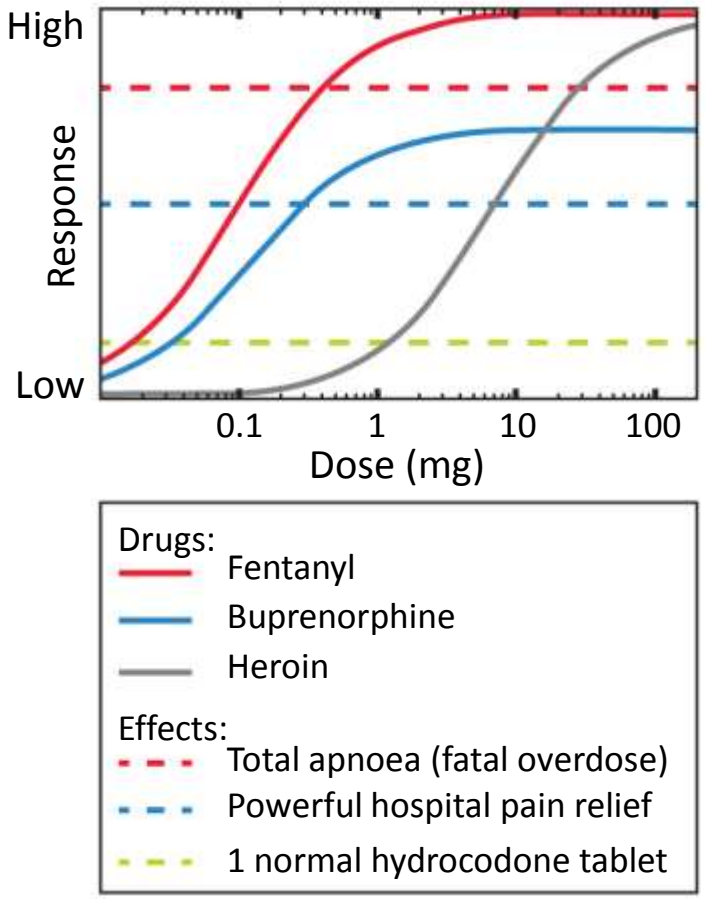
Opioids: Pharmacokinetic aspects

Drug	Dosing route	Pharmacokinetic aspects
Morphine	Oral (including slow release form), IV, IM, intrathecal	$t_{½}$ = 3–4 hr; converted to active metabolite (morphine-6-glucuronide)
Heroin	IV, IM, smoked, oral chasing	$t_{½}$ = <1 hr; partly metabolised
Methadone	Oral, IV, IM	$t_{½}$ = >24 hr; not active metabolite
Pethidine	Oral, IM	$t_{½}$ = 2–4 hr; active metabolite (norpethidine)
Buprenorphine	Sublingual, intrathecal, SC, IV, IM	$t_{½}$ = 40 hr
Fentanyl	IV, epidural, transdermal	$t_{½}$ = 1–2 hr
Codeine	Oral	Acts as pro-drug; metabolised to morphine and other active opioids

IM, intramuscular; IV, intravenous; $t_{½}$: the period of time required for the concentration or amount of drug in the body to be reduced by one-half

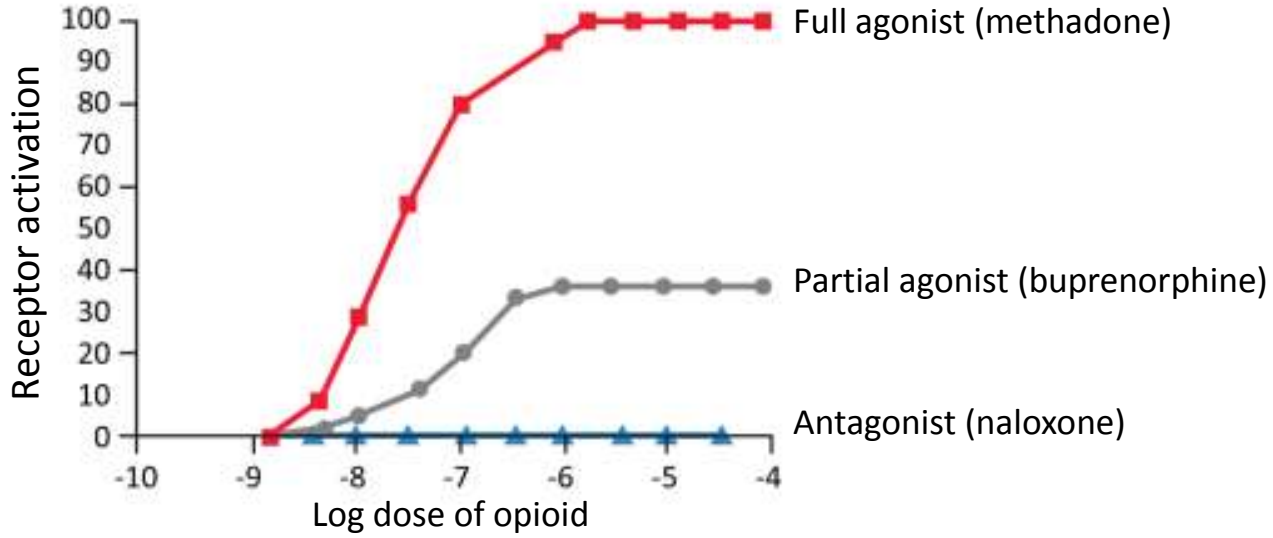
Buprenorphine pharmacodynamics

Dose-response curves for three opioid painkillers[1]



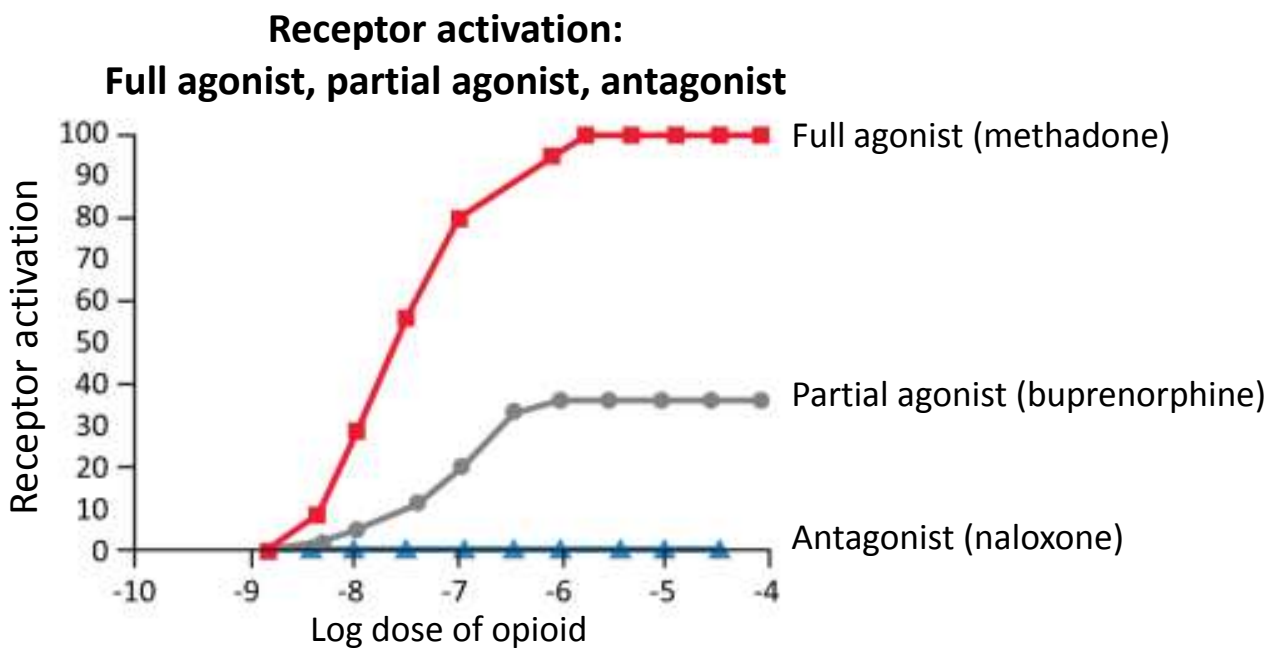
Opioid receptor	Ki (nM)	Agonist/antagonist
μ	1.5	Partial agonist
δ	6.1	Antagonist
K	2.5	Antagonist
Nociceptin or ORL1	77.4	Agonist

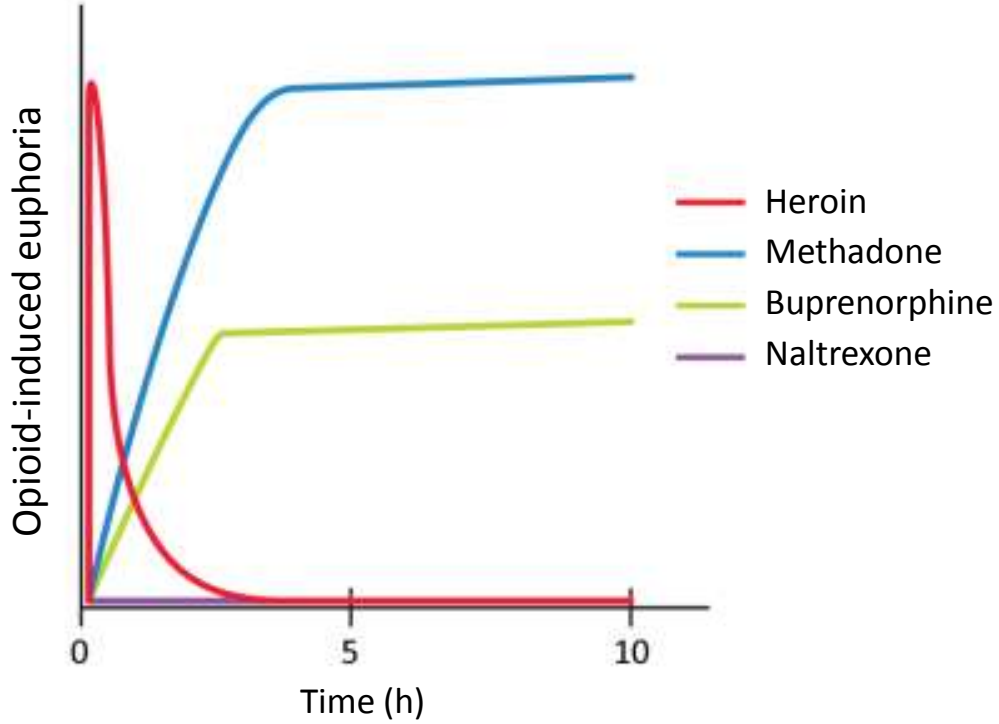
Receptor activation: Full agonist, partial agonist, antagonist



ORL1, opioid receptor-like 1. 1. Massachusetts Institute of Technology (2013). Drugs and the brain. 2. Khroyan TV *et al. Br J Pharmacol* 2015; 172(2):668–680. 3. Strain EC, ed. Use of buprenorphine in the pharmacologic management of opioid dependence: a curriculum for physicians. SAMHSA. 2001.

Euphoria and tolerance development is a function of ON-OFF effect and full agonist properties





National Institute on Drug Abuse (NIDA)-Center for Behavioral Health Statistics and Quality (CBHSQ), 2011.

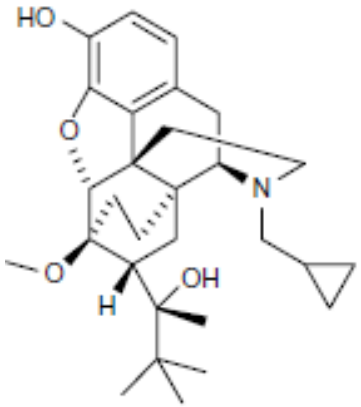
Question
Compared to full μ opioid receptor agonists, buprenorphine shows:

1. Less respiratory depression but similar reinforcing effects
2. Less respiratory depression and lower reinforcing effects
3. Similar respiratory depression and similar reinforcing effects
4. Higher respiratory depression and higher reinforcing effects

Objective

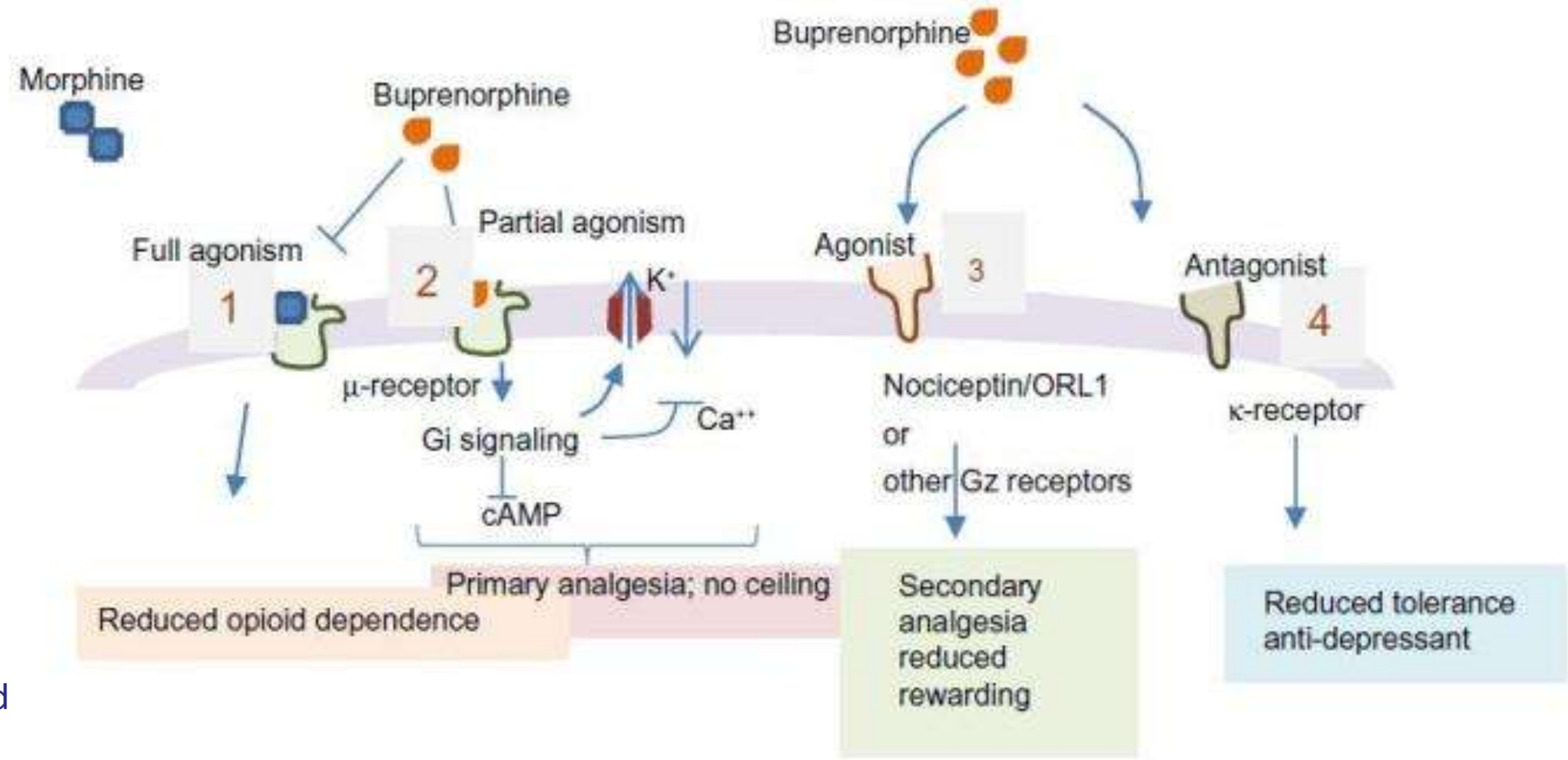
2 The pharmacodynamic effects of opioid receptor occupancy

Buprenorphine binds to NOP receptors



Buprenorphine is a semisynthetic opioid agent derived from thebaine[1]

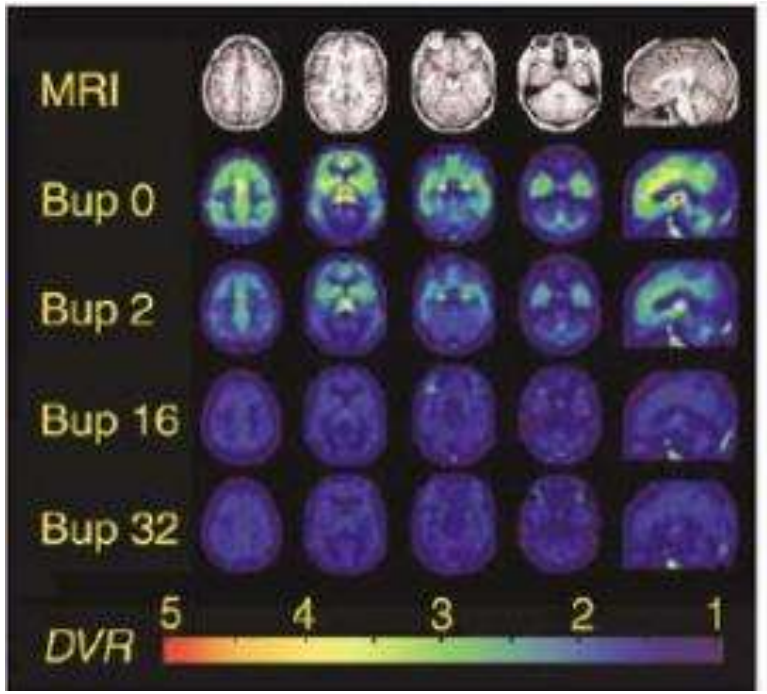
NOP plays a role in the regulation of reward and motivation pathways related to substance abuse[2]

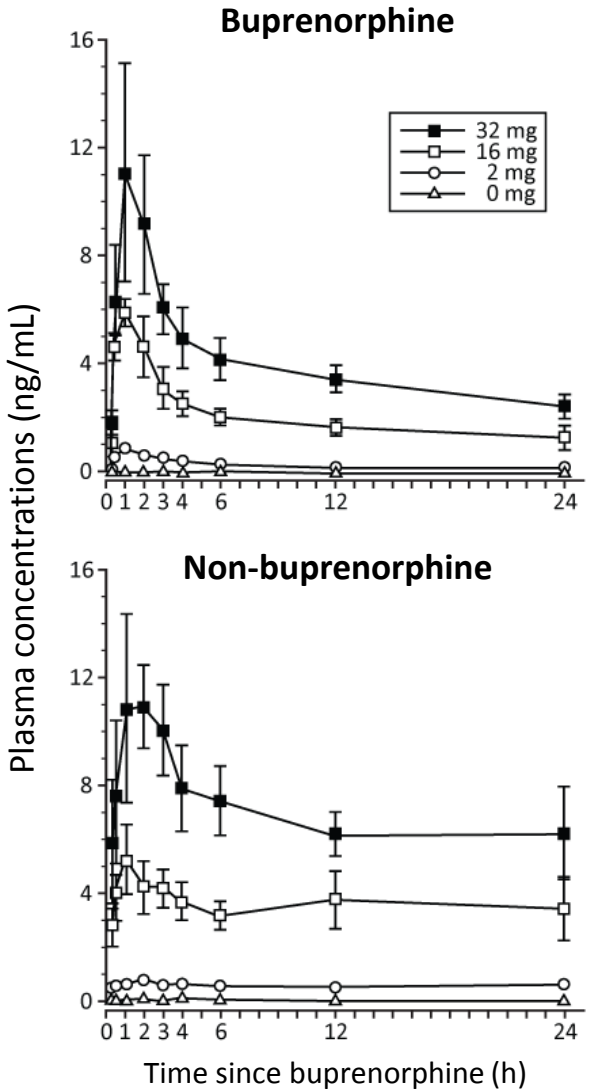


cAMP, cyclic adenosine monophosphate; NOP, nociceptin receptor; ORL1, opioid receptor-like 1

1. Khanna IK *et al. J Pain Res* 2015;8:859–70; 2. Zaveri NT. *Curr Top Med Chem* 2011;11:1151–6.

Buprenorphine occupation of μ-opioid receptors increases dose-dependently





- **High-dose (>16 mg) buprenorphine maintenance produces near-maximal receptor occupation**
- Higher receptor occupancy suppresses the effect of on-top hydromorphone use (“**opioid blockade**”)

Buprenorphine 32 mg may not be licensed in all countries. Please prescribe in accordance with local policies. MRI, magnetic resonance imaging.

Greenwald M *et al. Neuropsychopharmacology* 2003;28:2000–9.

μ-opioid receptor occupancy decreases over the 76 hours after buprenorphine 16 mg dosing

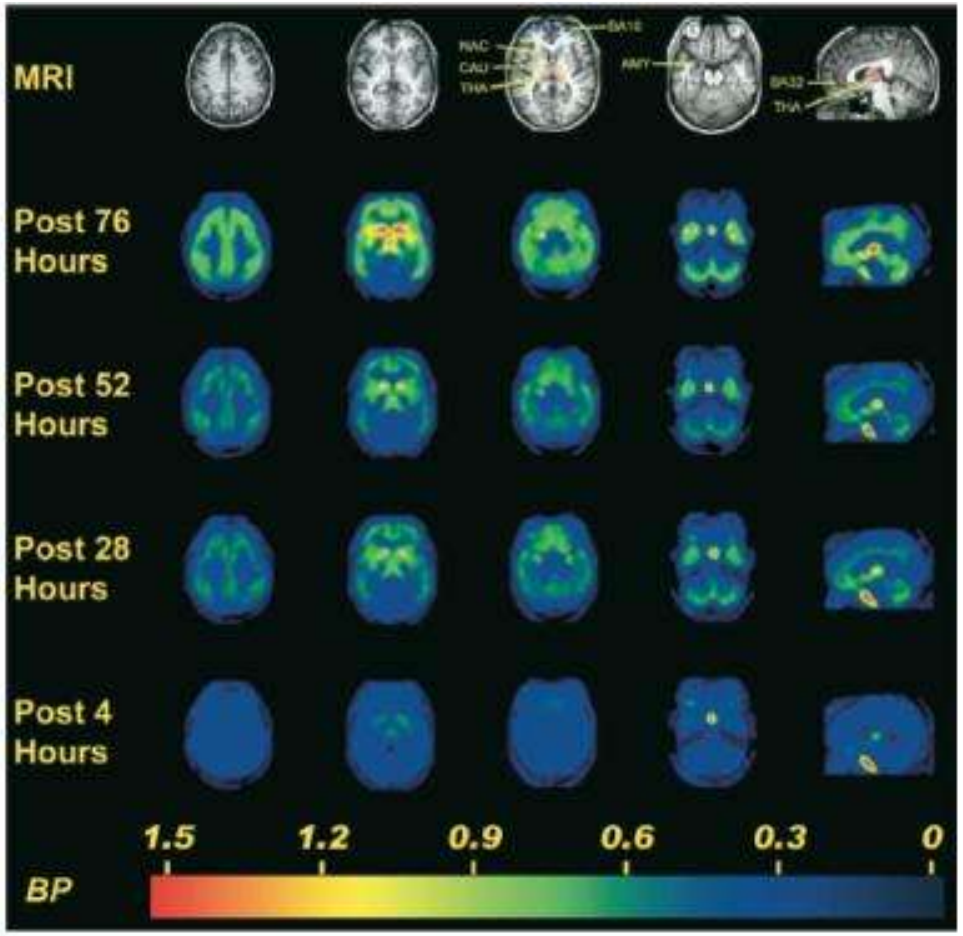
Mean whole-brain μ-opioid receptor availability after buprenorphine*

82%

67%

54%

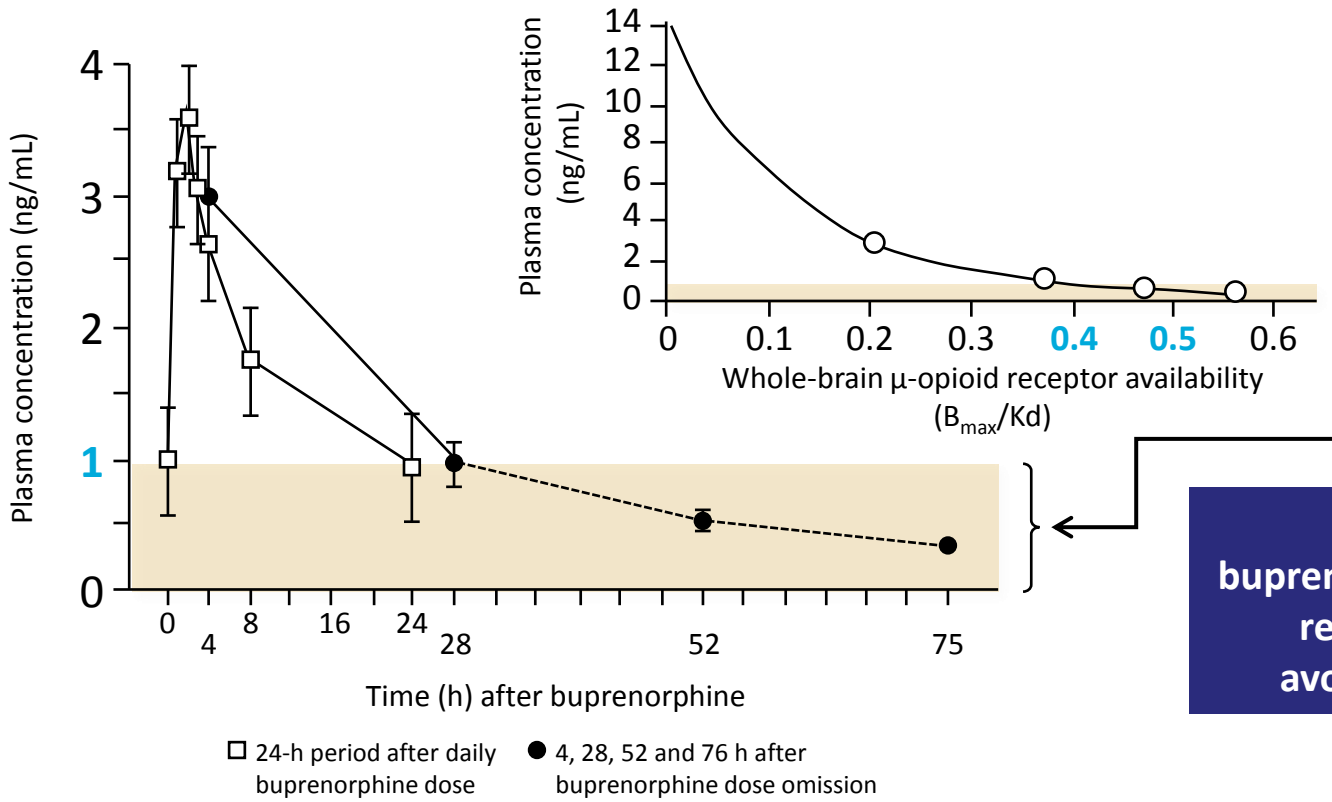
30%



*Relative to heroin-dependent volunteers maintained on placebo ; Buprenorphine/naloxone is licensed for doses of up to 24 mg. Buprenorphine is licensed for doses of up to 32 mg.
MRI, magnetic resonance imaging. Greenwald M *et al. Biol Psychol* 2007;61:101–10.

Plasma levels after buprenorphine 16 mg dosing correlate with μ-opioid receptor occupancy

C_{max} (ng/mL)	t_{max} (ng/mL)	$t_{1/2}$	24-h AUC (ng/mL*h)	78-h AUC (ng/mL*h)
3.9 (0.4)	2.2 (0.3)	21.7 (82)	41.9 (3.9)	75.4 (10.0)



Withdrawal symptoms occur at <40–50% receptor availability, corresponding to a buprenorphine plasma concentration of <1 ng/mL

With 16 mg dosing, buprenorphine plasma concentrations remain at >1 ng/mL per 24 h, avoiding withdrawal symptoms

AUC, area under the curve; C_{max}, maximum plasma concentration; t_{max}, time to reach C_{max}; $t_{1/2}$, half life

Greenwald M *et al. Biol Psychol* 2007;61:101–10.

Buprenorphine 16 mg: μ-opioid receptor occupancy over time

		Changes in μ-Opioid Receptor Availability (B_{max}/Kd)				
Brain region	**BUP Placebo**	**4 h**	**28 h**	**52 h**	**76 h**	**Time (*F* Test)**
Whole brain	**0.69 (0.01)**	**0.21 (0.02)** 29.8%	**0.37 (0.03)** 53.7%	**0.47 (0.03)** 67.4%	**0.57 (0.03)** 81.7%	**48.50 p<0.0001**
Subgenual anterior cingulate (BA25)	**1.39 (0.04)**	**0.43 (0.06)** 30.8%	**0.83 (0.07)** 60.1%	**1.04 (0.10)** 75.3%	**1.30 (0.10)** 93.8%	**35.45 p<0.0001**
Nucleus accumbens	**2.09 (0.12)**	**0.65 (0.07)** 30.9%	**1.27 (0.10)** 60.9%	**1.51 (0.10)** 72.2%	**1.80 (0.07)** 86.0%	**53.55 p<0.0001**
Rostral anterior cingulate (BA 32)	**1.56 (0.04)**	**0.41 (0.06)** 26.6%	**0.85 (0.08)** 54.5%	**1.06 (0.09)** 67.7%	**1.33 (0.09)** 84.9%	**44.01 p<0.0001**
Prefrontal cortex (BA 10)	**1.19 (0.03)**	**0.34 (0.05)** 28.6%	**0.64 (0.06)** 53.8%	**0.83 (0.06)** 69.5%	**1.01 (0.06)** 84.4%	**44.37 p<0.0001**
Caudate nucleus	**1.90 (0.15)**	**0.52 (0.06)** 27.5%	**1.03 (0.09)** 54.1%	**1.28 (0.11)** 67.5%	**1.53 (0.10)** 80.5%	**48.17 p<0.0001**
Amygdala	**1.57 (0.08)**	**0.42 (0.05)** 26.5%	**0.87 (0.08)** 55.1%	**1.03 (0.08)** 65.4%	**1.24 (0.09)** 78.7%	**48.24 p<0.0001**
Thalamus	**1.84 (0.08)**	**0.56 (0.05)** 30.3%	**0.99 (0.07)** 54.0%	**1.20 (0.08)** 65.5%	**1.41 (0.07)** 76.5%	**43.13 p<0.0001**

- Receptor occupancy >80% prevents the significant euphoric effects and respiratory depression elicited by on-top oxycodone (24 mg) administration i.e. blockade effect
- Receptor occupancy <40–50% – withdrawal signs appear

Blockade of opioid reward and craving may require higher doses (≥16 mg) than those needed to suppress withdrawal

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Review

Buprenorphine maintenance and *mu*-opioid receptor availability in the treatment of opioid use disorder: Implications for clinical use and policy

Mark K. Greenwald[a,*], Sandra D. Comer[b], David A. Fiellin[c]

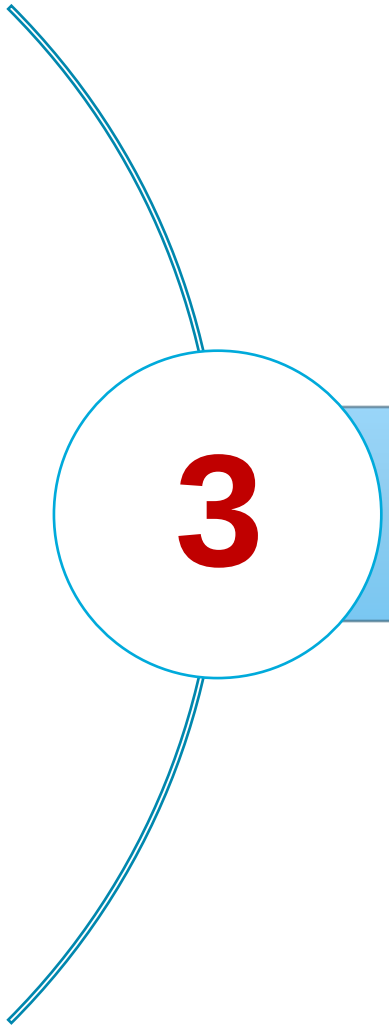
- Suppression of withdrawal appears to require ≤50% of μ-opioid receptor availability
- For most patients, this requires single daily buprenorphine doses of 4 mg

- Blockade of the reinforcing and subjective effects of typical doses of abused opioids require <20% μ-opioid receptor availability
- For most patients, this requires single daily buprenorphine doses of >16 mg

What % of receptor occupancy is generally needed to have an anti-craving effect?

1. >80%
2. 70–80%
3. 60–70%
4. 50–60%
5. 40–50%

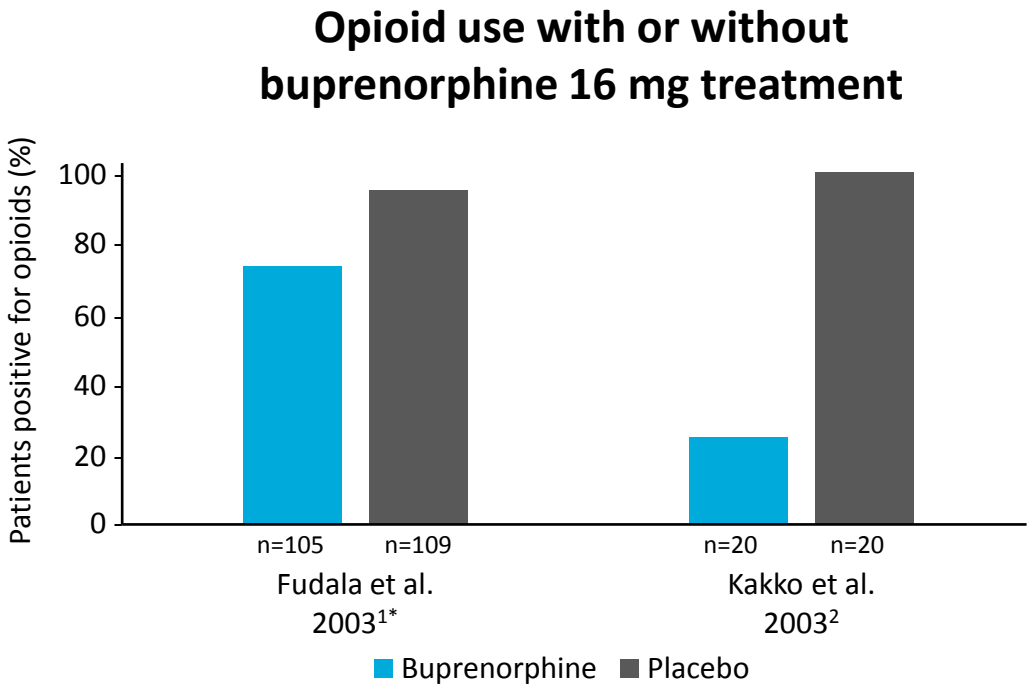
Objective

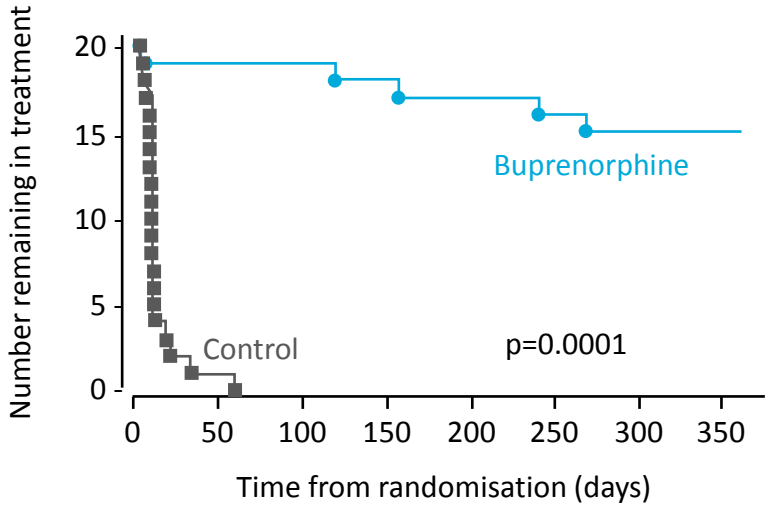


3

Linking buprenorphine pharmacology to clinical outcomes

Buprenorphine treatment reduces on-top use





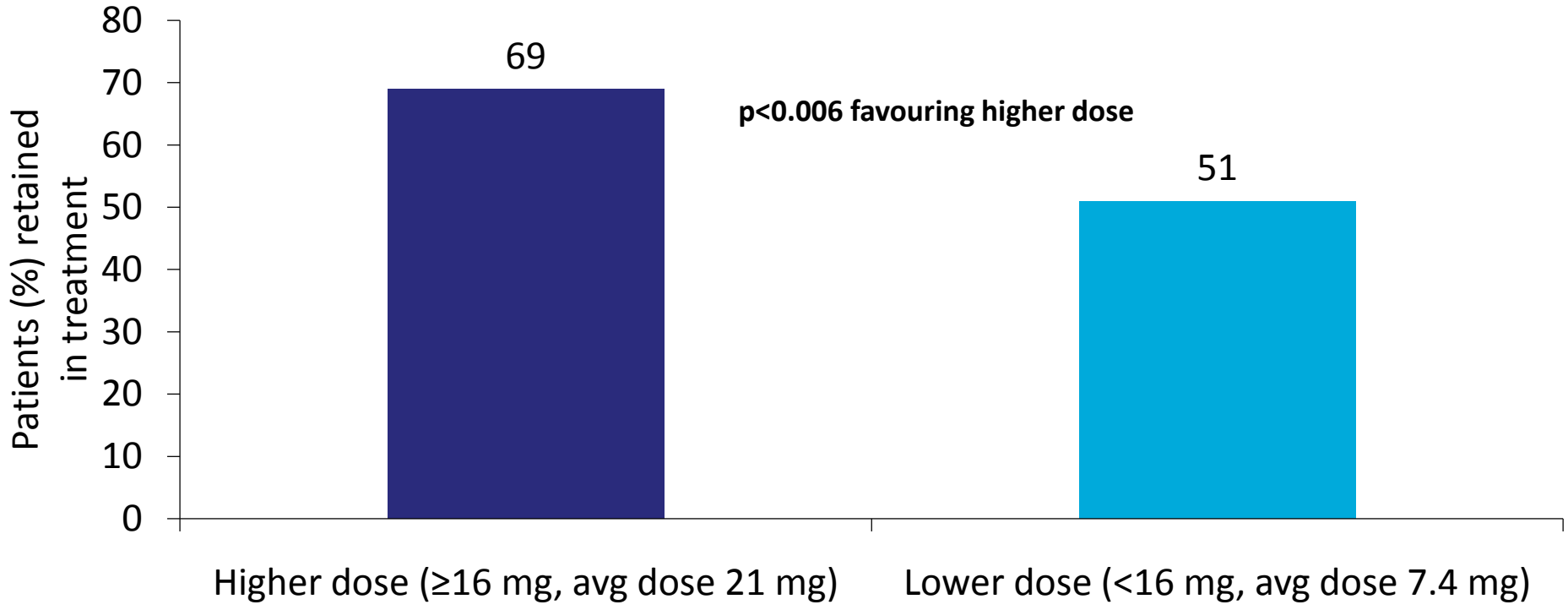
- Flexible dosing and buprenorphine doses ≤6 mg are less effective than methadone at retaining patients in treatment[3]

*Double blind phase terminated early due to greater efficacy of buprenorphine *vs* placebo

1. Fudala PJ *et al. N Engl J Med* 2003;349:949-58; 2. Kakko J *et al. Lancet* 2003;36:662–8; 3. Mattick RP *et al. Cochrane Database Syst Rev* 2014;(2):CD002207.

Strong evidence that high dose of buprenorphine is associated with better retention in treatment

- Meta-analyses of 21 RCTs conducted between 1960 and December 2010
- Treatment duration ranged from 3 to 48 weeks



Predictors of IOU: retention in treatment (↓ IOU); IOU, illicit opioid use; RCT, randomised controlled trial

Fareed A *et al*. *J Addict Dis* 2012;31:8–18.

Conclusions

- The unique characteristics of buprenorphine, namely, partial agonist effect, long duration of action and high binding affinity, make it an attractive treatment in opioid addiction

- Minimum μ-opioid receptor occupancy by buprenorphine of >40–50% prevents withdrawal symptoms but higher occupancy, typically >80% "blocks" euphoric effects from on-top opioid use and reduces craving symptoms

- Buprenorphine dose-dependently increases opioid receptor occupancy
  - High doses (≥16 mg) produce near-maximal occupancy, thereby providing an optimal occupation of opioid receptors

Improving quality of life through personalised care

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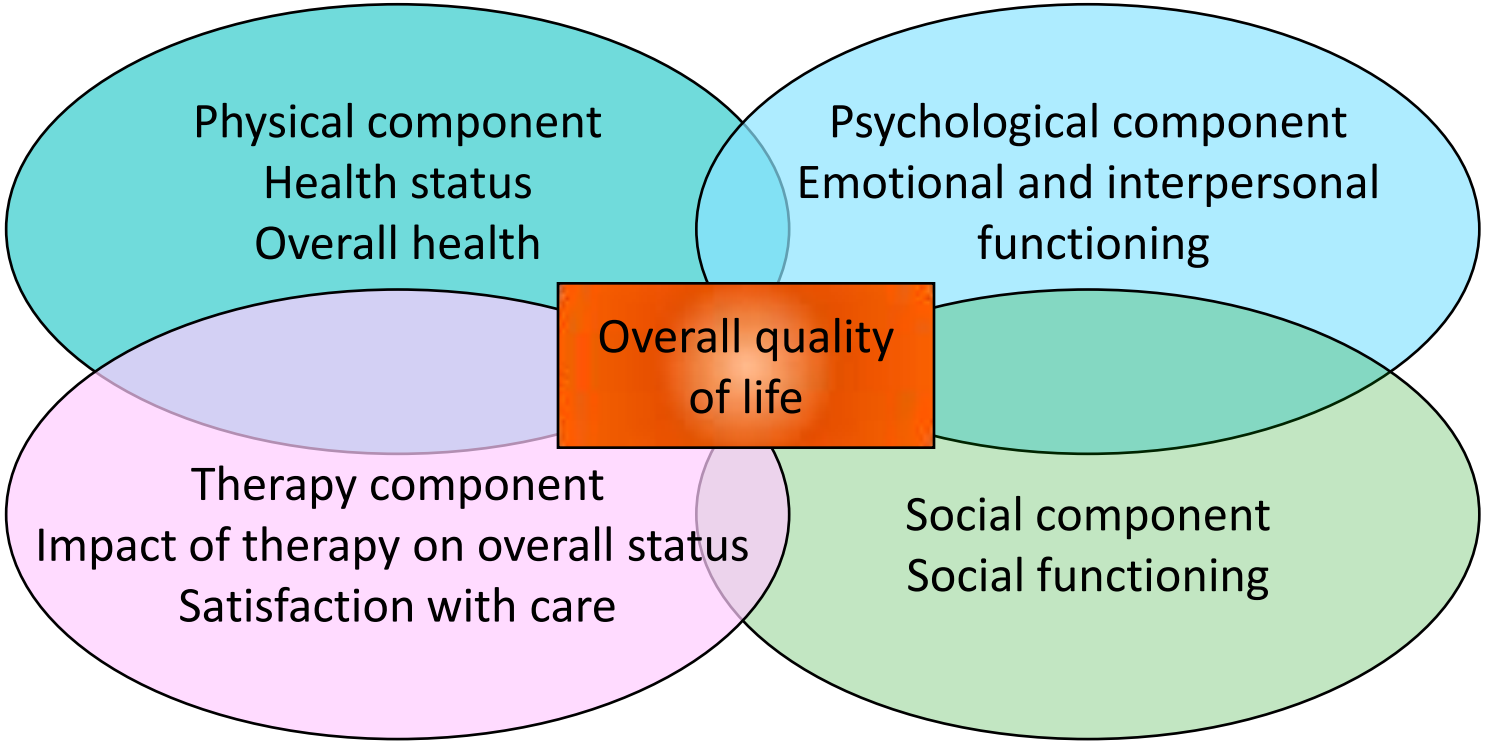
Date of Preparation: October 2017; Job Code: NBD-EU-P-1034-1708r

Disclosures

- Dr Melichar has received honoraria and travel expenses from Indivior for delivering this presentation
- Dr Melichar has also received funding from another pharmaceutical company, Britannia Pharmaceuticals, to speak at symposia and conferences

How is QoL defined?

- Defined in many ways, making measurement difficult
- The common principle is that it is **patient-centered** and mostly **subjective**

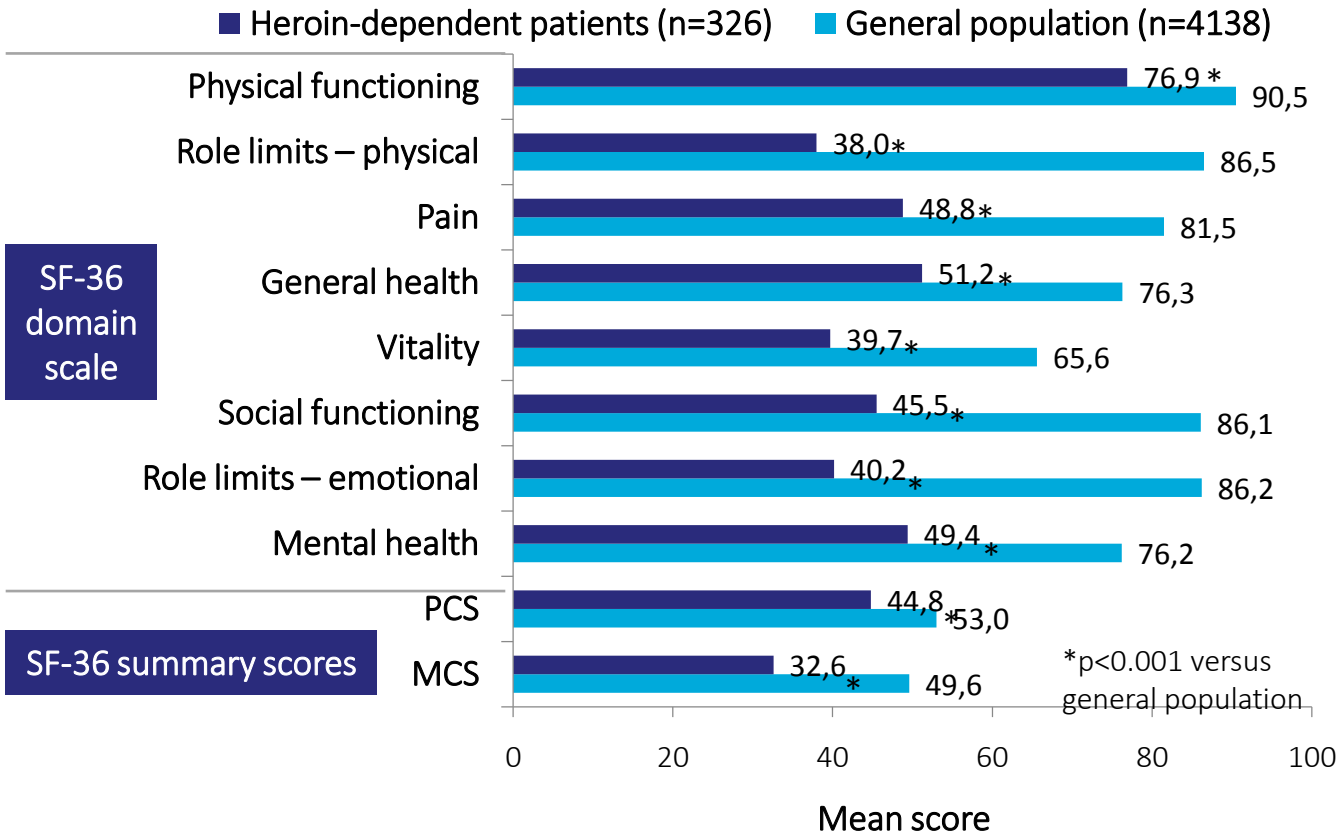


QoL, quality of life
Jan Melichar, personal experience

Patients with OUD have a reduced HRQoL

- OUD is a **chronic disorder** with multi-faceted and negative medical, psychological and social consequences **affecting various HRQoL domains**[1]
- Studies of HRQoL in patients with OUD have consistently found **worse scores for physical and mental domains** compared with the general population[3]
- Questionnaires such as SF-36 or QLQ or LQoLP are used for HRQoL assessment

Comparison of SF-36 mean (pre-treatment) baseline scores from heroin-dependent patients versus Australian population norms[2]

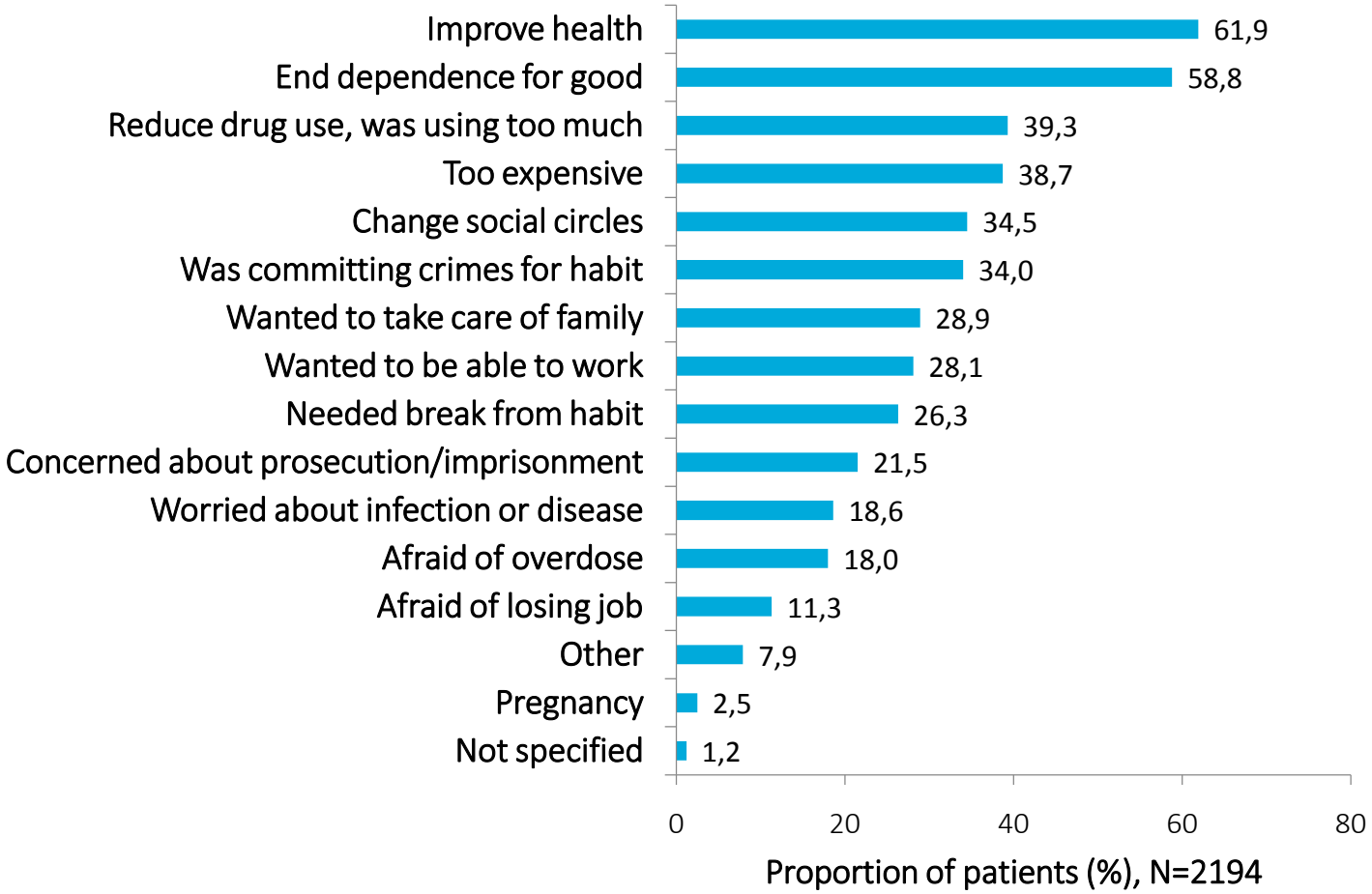


HRQoL, health-related quality of life; LQoLP, Lancashire Quality of Life Profile; OUD, opioid use disorder; MCS, mental component summary; PCS, physical component summary; QLQ, Quality of Life Questionnaire; SD, standard deviation; SF-36, short form 36

1. Cranmer H *et al. Value in Health* 2016;19:A387; 2. O'Brien S *et al. Addict Disord Their Treatment* 2006;5:155–64; 3. Griffin ML *et al. Am J Addict* 2015;24:308–14.

Why do people seek treatment for OUD?

- Data from EQUATOR analysis of 2,298 patients and 887 out-of-treatment opioid users from 10 European countries
- A key factor in the treatment of OUD is the ability and willingness of patients to enter and remain in treatment



EQUATOR, European Quality Audit of Opioid Treatment; OUD, opioid use disorder

Adapted from Benyamina A & Stöver H. *Heroin Addict Relat Clin Probl* 2012;14:65–80.

Interactive question

Based on 2017 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) data, approximately what percentage of patients with OUD across Europe are currently in treatment?

A. 30%

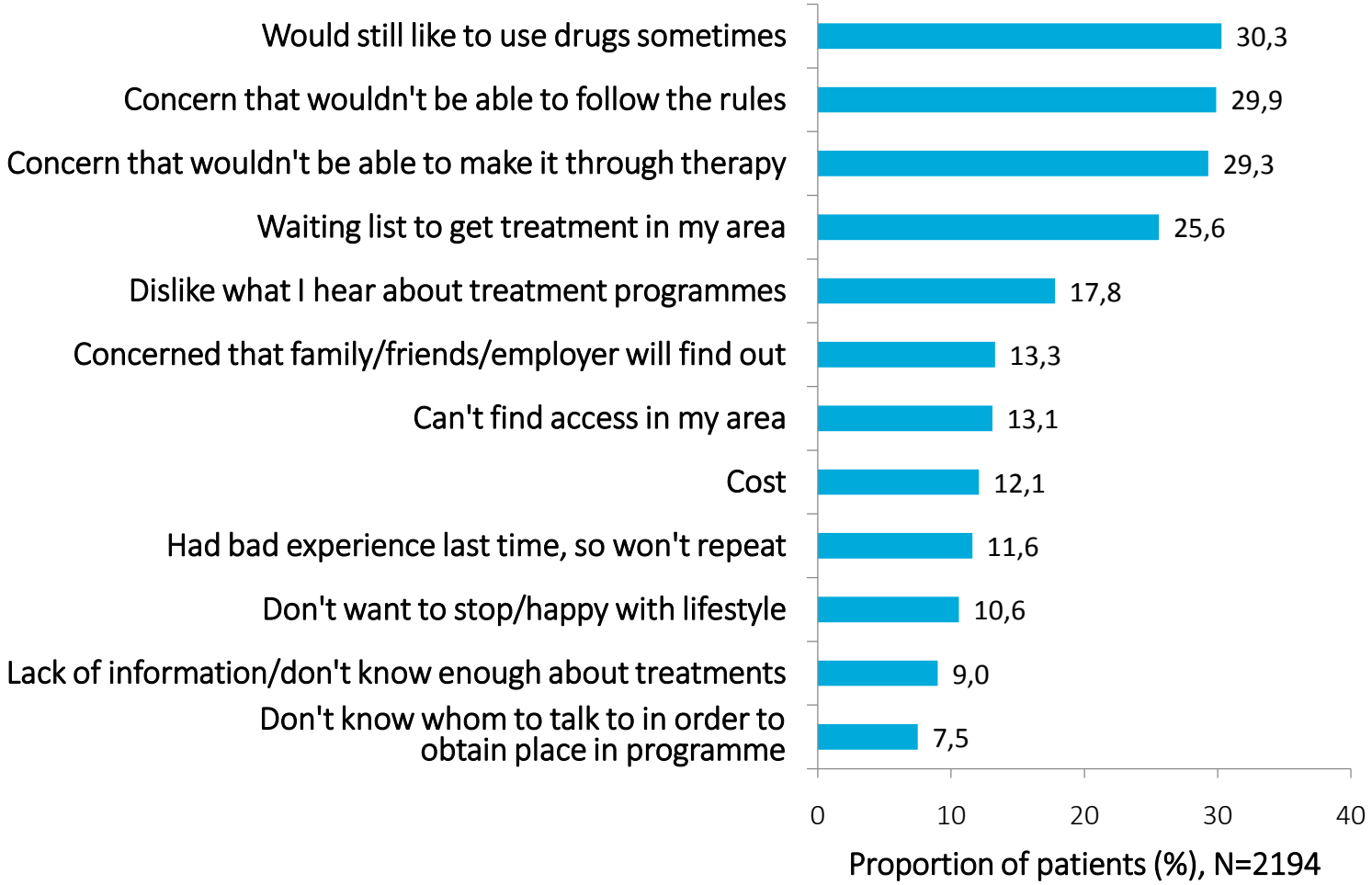
B. 40%

C. 50%

D. 60%

What are the barriers to seeking treatment for OUD?

- Data from EQUATOR analysis of 2,298 patients and 887 out-of-treatment opioid users from 10 European countries

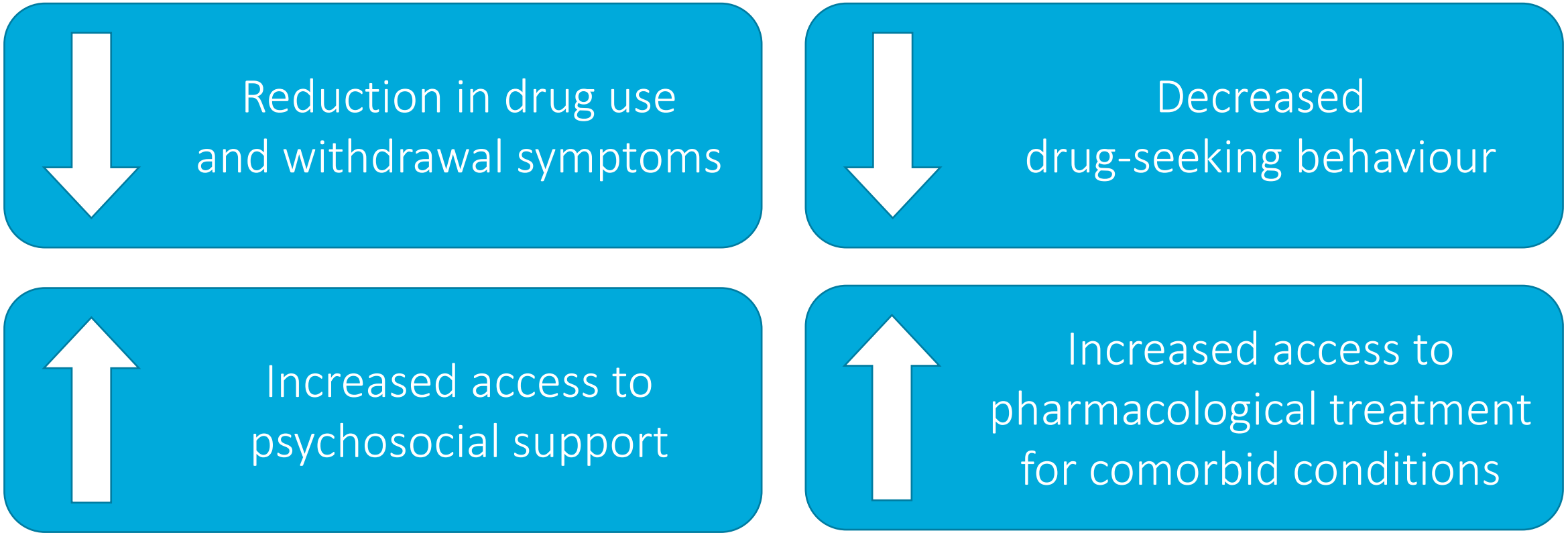


*Patients were asked to tick all that applied

EQUATOR, European Quality Audit of Opioid Treatment; OUD, opioid use disorder

Adapted from Benyamina A & Stöver H. *Heroin Addict Relat Clin Probl* 2012;14:65–80.

Role of OAT in improving patients' HRQoL



OAT, opioid agonist therapy; HRQoL, health-related quality of life

Nosyk B *et al. Drug Alcohol Depend* 2015;157:121–8.

Interactive question

In what proportion of your patients do you routinely try to ascertain quality of life indicators?

1. 20–40%
2. 40–60%
3. 60–80%
4. 80–100%

Impact of psychosocial interventions on QoL

- OATs are approved for use within a framework of medical, social and psychological support as part of comprehensive treatment programme
- Goal of psychosocial treatment is to help patients control cravings and remain abstinent, while also helping them cope with the emotional burden of OUD
- Systematic review of studies on the use of psychosocial interventions in conjunction with OAT

Methadone

- 14 studies provided support for the use of psychosocial interventions with methadone treatment
- 9 studies showed a significant effect on treatment attendance and drug use
- 7 studies showed a significant effect on psychosocial functioning

Buprenorphine

- Evidence to support the efficacy of psychosocial interventions with buprenorphine treatment was less robust
- 3 studies reviewed found a significant effect on treatment attendance and drug use
- 1 study found a significant effect on 12-step/self-help meeting attendance

OAT, opioid agonist therapy; OUD, opioid use disorder; QoL, quality of life

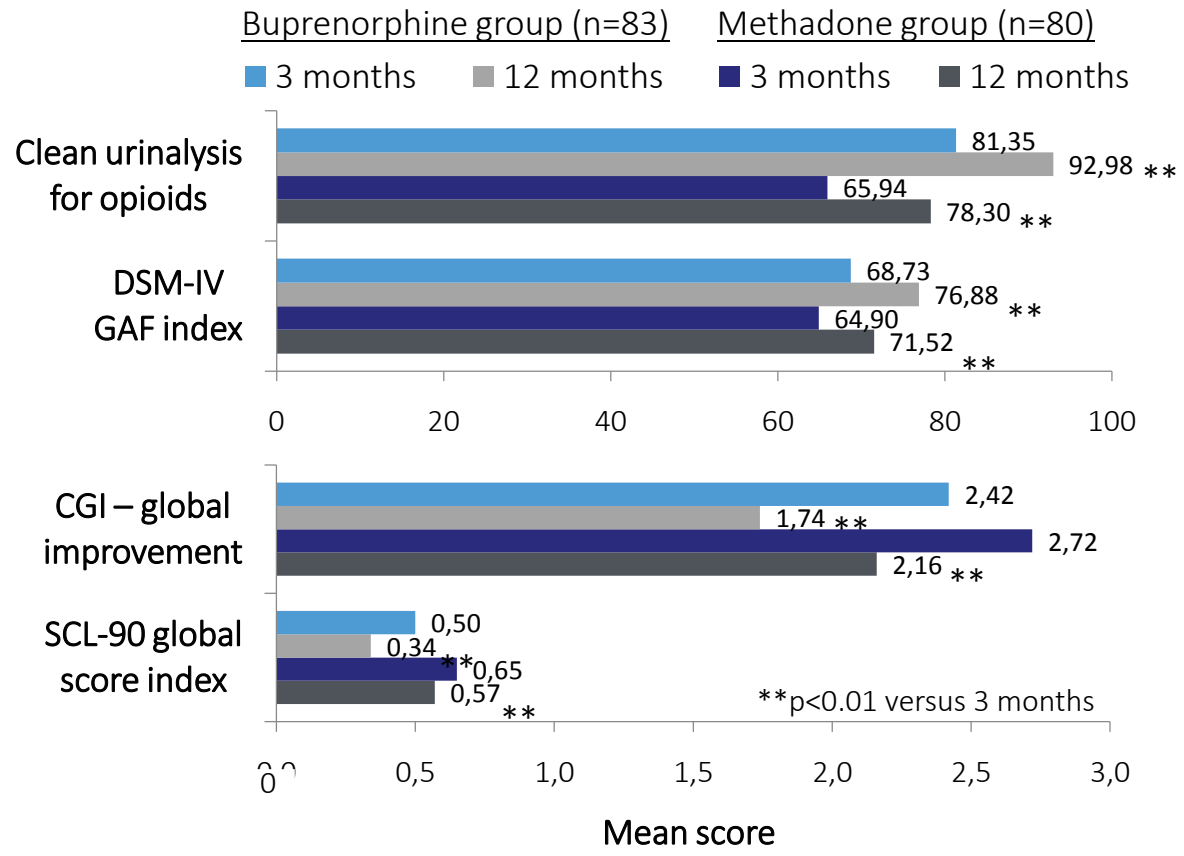
Dugosh K *et al. J Addict Med* 2016;10:91–101.

Improvement in QoL following long-term treatment with buprenorphine or methadone

- Cohort study of patients with OUD on buprenorphine (n=106) or methadone (n=107) followed from month 3 to month 12 of treatment
- At 3 months, the total QLQ score was significantly greater with buprenorphine *vs* methadone (299.62 *vs* 258.96, respectively; p=0.003)
- At 12 months, retention rates were comparable (78.3% *vs* 74.6% for buprenorphine and methadone, respectively)
- At 12 months, statistically significant improvements in reduction in opioid use, psychiatric status, and general QoL* were observed with both treatments

*Assessed using the CGI, GAF Scale, SCL-90 and QLQ

Comparison of QoL scores from buprenorphine- or methadone-treated patients



OUD, opioid use disorder; QLQ, Quality of Life Questionnaire; QoL, quality of life; SD, standard deviation; SF-36, short form 36

Maremmani I *et al. J Subst Abuse Treat* 2007;33:91–8.

Optimising dosing in patients on OAT

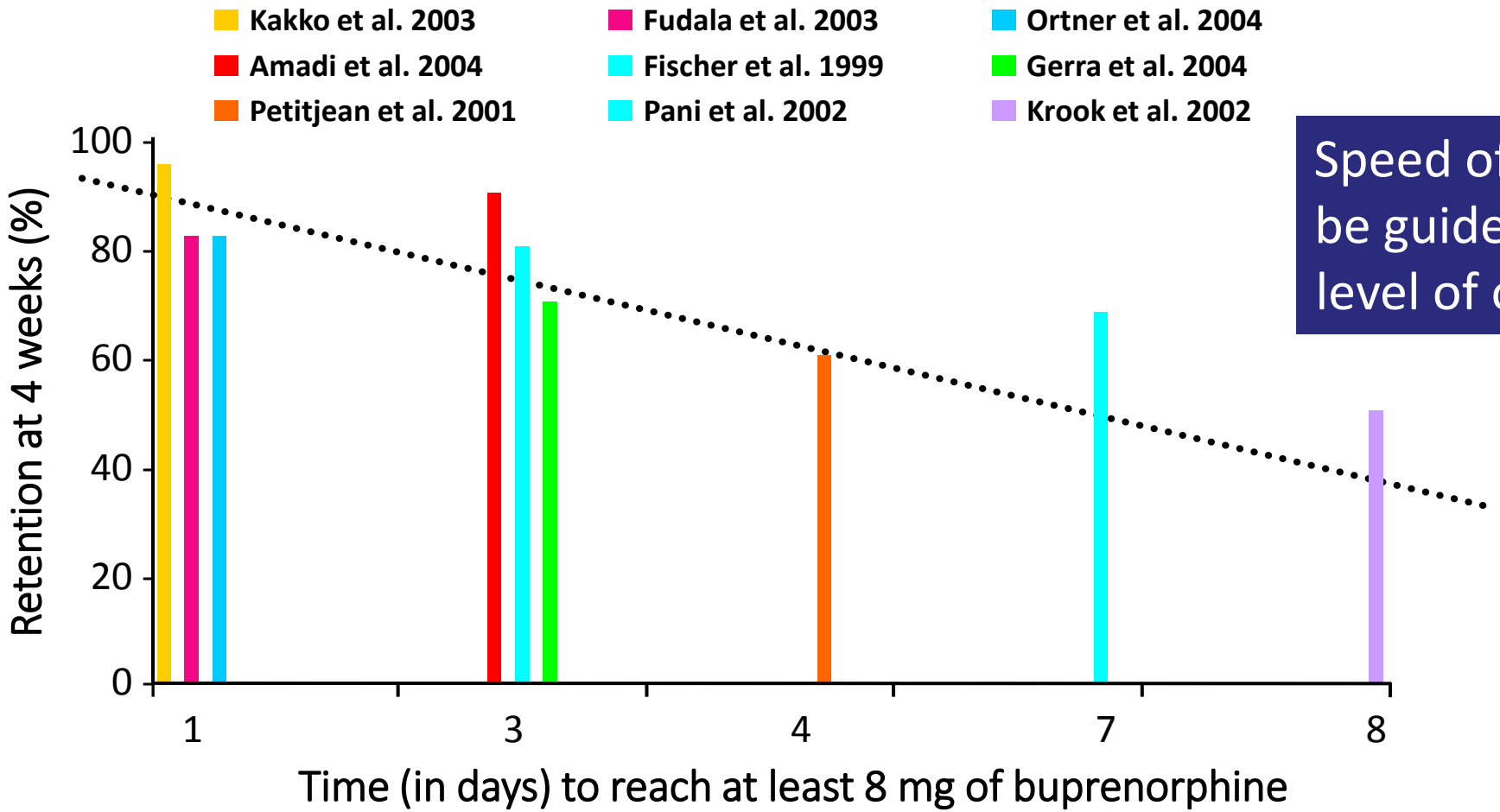
'The ACMD wishes to state that service users should receive opioid substitution medication doses in line with UK clinical guidelines, and sub-optimal opioid prescribing is unlikely to help service users stop illicit heroin use and is ***associated with poorer outcomes****'*

ACMD

Advisory Council on the Misuse of Drugs

QoL, quality of life; Advisory Council on the Misuse of Drugs (ACMD). How can Opioid Substitution Therapy (and drug treatment and recovery systems) be optimised to maximise recovery outcomes for service users. October, 2015.

Rapid induction with buprenorphine improves initial retention in treatment and optimal dosing reduces craving



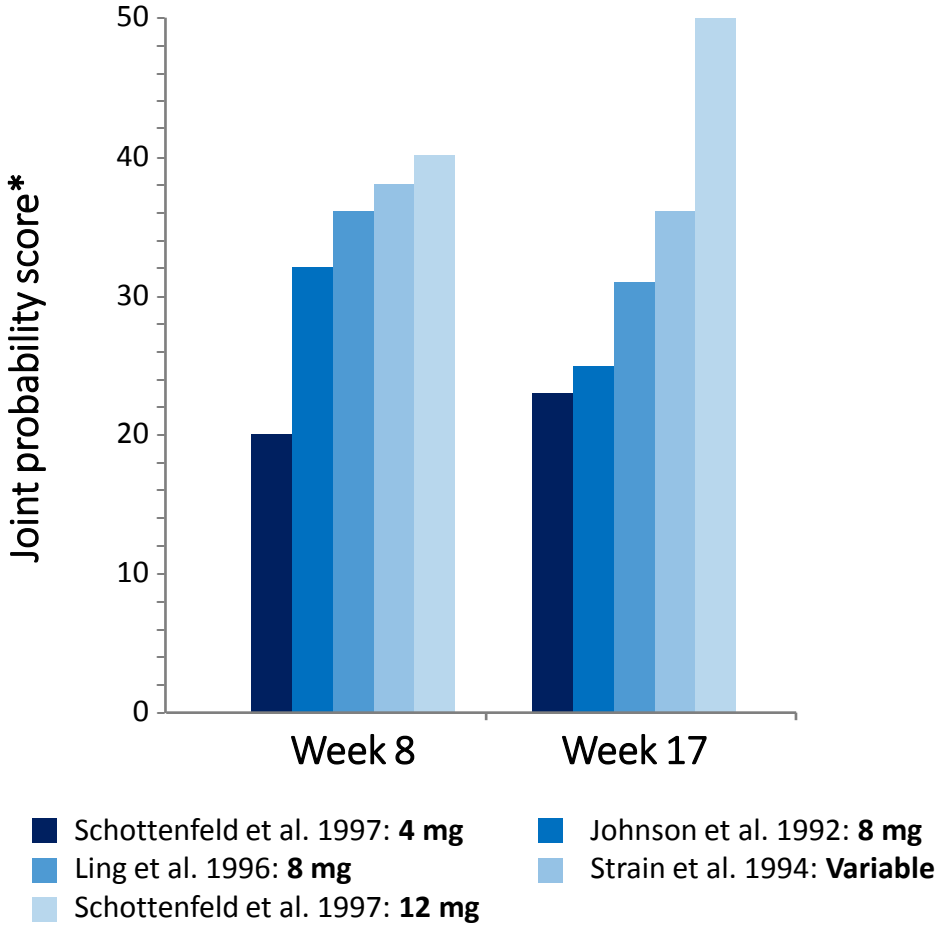
Speed of induction should be guided by the patient's level of opioid withdrawal

Adapted from Bacha J *et al. Heroin Addict Relat Clin Probl* 2010;12:9–19.

Optimal dosing of OAT prevents relapse

- Higher doses of buprenorphine or methadone are significantly more effective than low doses at reducing illicit heroin use[1]
- Higher maintenance doses of buprenorphine lead to improved outcomes[2]

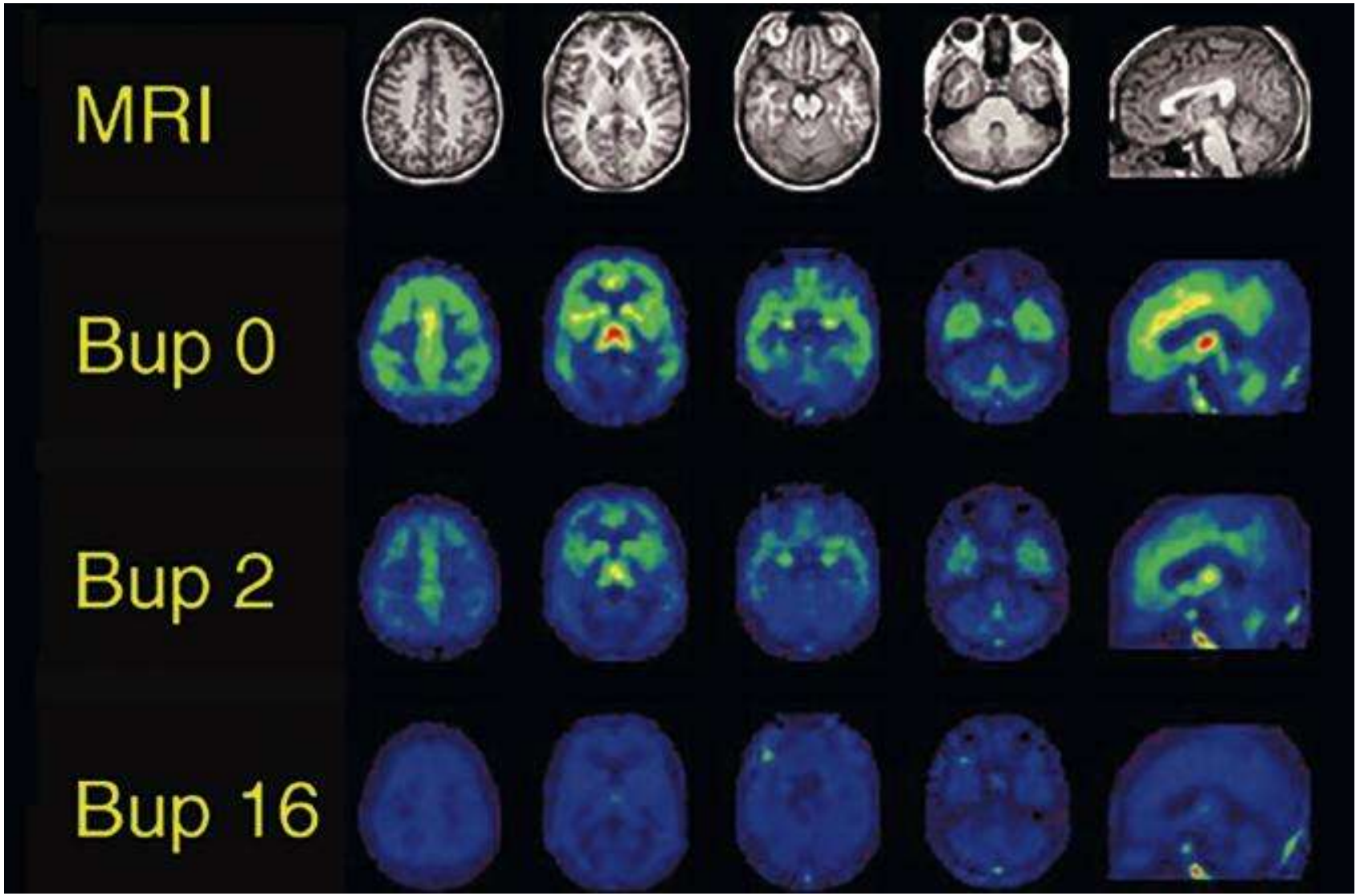
Higher maintenance doses of buprenorphine are associated with higher retention and increased abstinence from illicit opioids[3]



*Joint probability score: measure of the likelihood of patients remaining in treatment and being drug-free; OAT, opioid agonist therapy

1. Farré M *et al. Drug Alcohol Depend* 2002;65:283–90; 2. Fareed J *et al. J Addict Dis* 2012;31:8–18; Figure adapted from Bacha J *et al. Heroin Addict Relat Clin Probl* 2010;12:9–19.

Buprenorphine receptor occupancy – importance of 16 mg dose



Relative to placebo, buprenorphine 16 mg reduced μ-opioid receptor availability in the brain

↓

Reduced withdrawal symptoms and cravings

↓

Clarity of thought & other HRQoL benefits

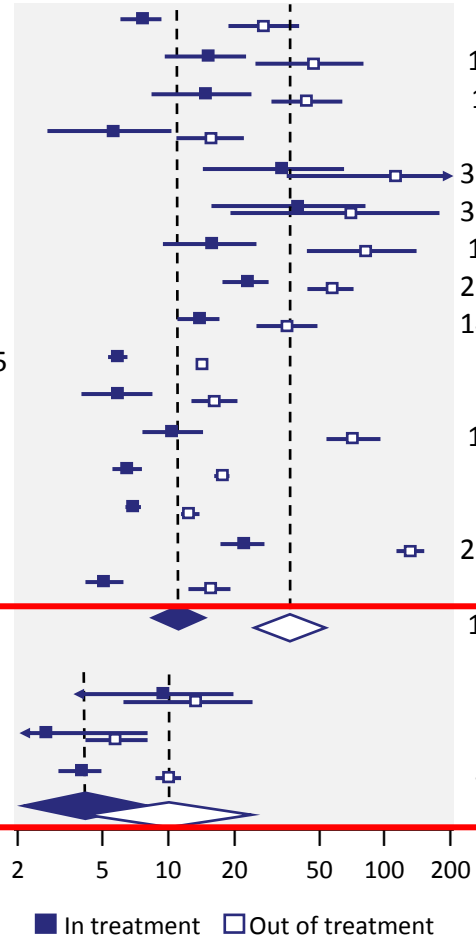
HRQoL, health-related quality of life.

Greenwald M. *Neuropsychopharmacology* 2003;28:2000–9.

Factors impacting on **drug-related deaths**: Medically-assisted treatment

- 122,885 patients treated with methadone over 1.3–13.9 years
- 15,831 people treated with buprenorphine over 1.1–4.5 years
- Retention in methadone and buprenorphine treatment was associated with **substantial reductions in the risk for all-cause and overdose mortality**

	No of deaths/ person years		All-cause mortality rate/ 1000 person years (95% CI)	All-cause mortality rate/ 1000 person years (95% CI)	
Methadone	**In treatment**	**Out of treatment**		**In treatment**	**Out of treatment**
Gearing et al. 1974	110/14,474	33/1170		7.6 (6.2 to 9.2)	28.2 (19.4 to 39.6)
Cushman 1977	25/1655	14/297		15.1 (9.8 to 22.3)	47.1 (25.8 to 79.1)
Grönbladh et al. 1990	16/1085	32/740		14.8 (8.4to 23.9)	43.2 (29.6 to 61.0)
Caplehom et al. 1994	11/1975	36/2279		5.6 (2.8 to 10.0)	15.8 (11.1 to 21.9)
Fugelstad et al. 1995	8/242	5/45		33.1 (14.3 to 65.1)	111.1 (36.1 to 259.3)
Fugelstad et al. 1998	7/177	4/57		39.5 (15.9 to 81.4)	69.9 (19.1 to 179.0)
Scherbaum et al. 2002	18/1114	14/172		16.2 (9.6 to 25.5)	81.4 (44.5 to 136.6)
Fugelstad et al. 2007	77/3354	74/1311		23.0 (18.1 to 28.7)	56.5 (44.3 to 70.9)
Clausen et al. 2008	90/6450	46/1303		14.0 (11.2 to 17.1)	35.3 (25.9 to 47.1)
Dagenhardt et al. 2009	648/111,538	1510/105,735		5.8 (5.4 to 6.3)	14.3 (13.6 to 15.0)
Cornish et al. 2010	30/5129	71/4288		5.8 (4.0 to 8.3)	16.6 (12.9 to 20.9)
Peles et al. 2010	42/3985	52/727		10.5 (7.6 to 14.2)	71.5 (53.4 to 93.8)
Evans et al. 2015	163/25,277	848/48,122		6.4 (5.5 to 7.5)	17.6 (16.5 to 18.8)
Kimber et al. 2015	636/92,792	563/45,265		6.9 (6.4 to 7.5	12.4 (11.4 to 13.5)
Nosyk et al. 2015	89/3979	206/1582		22.4 (18.0 to 27.5)	130.2 (113.0 to 149.3)
Cousins et al. 2016	115/22,648	98/6247		5.1 (4.2 to 6.1)	15.7 (12.7 to 19.1)
Overall				11.3 (8.4 to 15.2)	36.1 (24.5 to 53.3)
Buprenorphine					
Cornish et al. 2010	7/740	10/751		9.5 (3.8 to 19.5)	13.3 (6.4 to 24.5)
Reece 2010	3/1119	40/6911		2.7 (0.6 to 7.8)	5.8 (4.1 to 7.9)
Kimber et al. 2015	87/21,936	314/31,239		4.00 (3.2 to 4.9)	10.1 (9.0 to 11.2)
Overall				4.3 (2.1 to 8.9)	9.5 (3.9 to 23.4)



CI, confidence interval; OAT, opioid agonist therapy

Adapted from Sordo L *et al. BMJ* 2017;357:j1550.

Summary

- OAT plays a key role in improving HRQoL by reducing drug use, withdrawal symptoms and drug-seeking behaviours, and increasing access to psychosocial support and treatment for comorbid conditions
- Routine assessment of HRQoL can add an important dimension to overall evaluation of patients' response to OAT
- A personalised approach to care is needed with the optimal treatment strategy taking into account the patient's complete medical and psychiatric history
  - Optimised dosing with buprenorphine reduces withdrawal symptoms and cravings, can improve initial retention in treatment and prevent relapse….

…..leading to improved HRQoL

HRQoL, health-related quality of life; OAT, opioid agonist therapy; OUD, opioid use disorder

Voting question

Do you routinely measure craving in your daily clinical practice?

- Yes
- No

Interactive discussion


Please remember
to complete your
evaluation form
INDIVIOR
Focus on you.